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14. ABSTRACT

Disease persistence is the main issue faced by CML patients on therapy with imatinib and eradication of persistent malignant cells will be critical for the long-term success of kinase inhibitor therapy. Mechanisms underlying acquired resistance to imatinib have been extensively studied and the manner by which mutations of the Bcr-Abl kinase domain can reduce or eliminate sensitivity of CML cells to imatinib has been well characterized. Disease persistence in responding patients, in contrast, is still poorly understood. We sought to identify and extensively characterize hematopoietic stem cells responsible for disease persistence and explore their mechanisms of imatinib resistance. Using in vitro culture of primary CML progenitor cells, we identified both quiescent and cycling cells capable of surviving in the presence of imatinib. We observed inhibition of tyrosine phosphorylation by imatinib in surviving cells, suggesting a Bcr-Abl independent mechanism of survival. To apply information gained from in vitro culture to persistent cell populations in treated CML patients, we attempted to isolate Bcr-Abl positive cells from patients in cytogenetic remission. Although persistent CML cells may reside within the stem cell compartment, techniques of stem cell enrichment did not lead to enrichment of CML cells. We are therefore developing techniques for Bcr-Abl-specific detection to facilitate these studies, including creation of a Bcr-Abl junction-specific antibody, development of a Bcr-Abl mRNA junction-specific molecular beacon and analysis of potential markers of CML cells. Evaluation of the utility of these techniques in primary cells is ongoing. The detailed analysis of primary samples is technically challenging, but is essential for an understanding of disease persistence and may allow identification of novel drug targets or methods to sensitize resistant cells to imatinib or alternative Bcr-Abl kinase inhibitors.

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INTRODUCTION

Targeted therapy with the Abl kinase inhibitor imatinib (Gleevec) induces hematologic and cytogenetic remission in the majority of chronic phase CML[1]. Very few patients, however, have undetectable leukemic cells when more sensitive detection techniques are used and the majority of these patients relapse if imatinib is discontinued[2]. Thus, disease persistence is the main issue faced by the majority of CML patients on therapy with imatinib and eradication of persistent malignant cells will be critical for the long-term success of kinase inhibitor therapy. As Bcr-Abl positive cells persist for up to five years, thus far, this argues that some imatinib-resistant populations are hematopoietic stem cells (HSC) with long-term self-renewal capacity. In fact, $CD34^+$ cells from complete cytogenetic remission (CCR) patients are enriched for Bcr-Abl^+ cells[3]. Many mechanisms of disease persistence have been proposed, including drug efflux[4-8], Bcr-Abl kinase domain mutations[9], Bcr-Abl amplification[10], stem cell quiescence[11,12] and protection by the bone marrow microenvironment[13]. Evidence that these processes apply to persistent cells is limited and mostly circumstantial and thorough analysis of resistance mechanisms in persistent cells from CCR patients has not been done. The goals of this project are to identify and extensively characterize hematopoietic stem cells responsible for disease persistence and explore their mechanisms of imatinib resistance.

The specific aims are: 1) To determine if Bcr-Abl is active in HSC populations that survive imatinib treatment and to determine which mechanisms contribute to the survival of these cells; and 2) To determine which subpopulations of cells are persistently Bcr-Abl^+ in imatinib treated CML patients that have achieved CCR.

BODY

<u>Aim 1</u> – Determine if Bcr-Abl is active in HSC populations that survive imatinib treatment and to determine which mechanisms contribute to the survival of these cells

In vitro culture of CML stem cells with imatinib

Initially, we wished to determine whether Bcr-Abl is active in primary CML cells that survive culture in imatinib. For these studies, bone marrow and leukapheresis samples from seven newly diagnosed, imatinib-naïve chronic phase CML patients and two normal samples were used. Mononuclear cells, isolated by Ficoll centrifugation, were depleted, by immunomagnetic separation, of cells expressing lineage markers. Lin^- cells were cultured in serum free medium either without cytokines or with a five cytokine cocktail (100ng/mL Flt ligand, 100ng/mL SCF, 20ng/mL IL-3, 20ng/mL IL-6, 20ng/mL G-CSF) in the presence of imatinib for four days as described[12]. Initial experiments were done in the absence of cytokines, a culture condition that supports the growth of primitive Bcr-Abl^+ but not normal cells[14]; however, we found by culturing normal samples that a fraction of normal bone marrow Lin^- cells were capable of surviving in these culture conditions (Table 1). Additional experiments were therefore done in the presence of cytokines to more closely represent native conditions. Results observed in both culture conditions are presented here. Cell density was monitored daily to determine the degree of cell expansion. Both in the absence and presence of cytokines, Ph^+ cells were able to survive imatinib treatment (Tables 1,2).

Table 1. Cell growth, phenotype and cell cycle status of primary CML cells and normal bone marrow cultured in the presence or absence of imatinib (IM).

Sample	Culture Condition	Fold Cell Expansion	Ph^+
CML1	No Drug	1.6	95%
	Imatinib	0.14	9%
CML2	No Drug	2.7	Nd
	Imatinib	0.94	Nd
CML3	No Drug	2.1	96%
	Imatinib	0.4	93%
CML4	No Drug	0.5	98%
	Imatinib	0.57	97%
normal1	No Drug	0.44	0%
	Imatinib	0.34	0%
normal2	No Drug	0.2	0%
	Imatinib	0.28	0%

Additionally, in the presence of cytokines, all samples showed a net expansion of cells treated with imatinib and similar cell cycle status as their untreated counterparts (Table 2), indicating the capacity to proliferate in the presence of the inhibitor. Acridine Orange staining demonstrated a slight increase in the G_0 fraction with imatinib treatment in all samples; however, this only represented 17-31% of cells. This suggests that there are mechanisms of cell survival in addition to quiescence, as previously reported[12]. Cells were analyzed for expression of lineage specific markers and stem cell markers. Prior to culture, all samples were >90% Lin^- (not shown). Following culture there was an increase in expression of lineage markers and a decrease in CD34 expression. There was a greater decrease in Lin^-, $CD34^+$ and $CD133^+$ cells, in imatinib treated cultures indicating enhanced cell differentiation during the culture period (Table 2). This may be due to inhibition of Kit by imatinib, as we have observed in additional experiments that culture with SCF maintains an immature phenotype of primary CML cells (not shown).

Table 2. Cell growth, phenotype and cell cycle status of primary CML cells cultured in the presence or absence of imatinib (IM) in a five-cytokine cocktail.

Sample	Culture	Fold Cell expansion	Ph^+	Lin^-	$CD34^+$	$CD133^+$	G_0/G_1	G_0
CML5	-IM	4	97%	58%	59%	9%	75%	12%
	+IM	2.6	94%	41%	41%	5%	78%	17%
CML6	-IM	15	99%	55%	48%	10%	61%	4%
	+IM	4.9	99%	39%	42%	7%	67%	10%
CML7	-IM	9.5	100%	81%	83%	70%	75%	26%
	+IM	2.8	97%	75%	67%	56%	68%	31%

CML cells surviving imatinib treatment were analyzed for inhibition of Bcr-Abl activity. When sufficient cell numbers were available, this was done by western blotting for phosphotyrosine in untreated and treated cell lysates. Intracellular FACS for Bcr-Abl-specific targets P-CrkL, P-Abl and total P-tyr was explored as a means of analyzing small numbers of primary cells. In $CD34^+$ CML cells all three antibodies demonstrated target specificity; however, total phosphotyrosine was chosen for our studies based on superior signal relative to background (Figure 1).

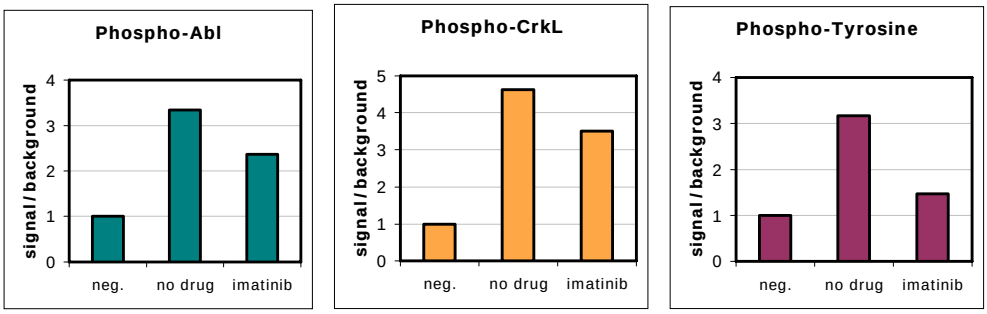

Figure 1. Intracellular FACS analysis of CML CD34+ cells using phospho-Abl (left), phospho-CrkL (middle) and total phosphotyrosine (right) antibodies. Signal relative to background is shown for cells incubated with or without 10μM imatinib.

Imatinib treated cells showed a dramatic inhibition of cellular phosphotyrosine levels (Figure 2A). This could be at least partially reversed by washing imatinib from the culture. Representative western blot and intracellular P-FACS are shown (Figure 2B,C). It is unclear whether incomplete restoration of phosphorylation upon washout is due to an overall decrease in Bcr-Abl activity in imatinib treated cells, or incomplete removal of drug. These results indicate that a fraction of CML progenitors can survive and proliferate in conditions that inhibit Bcr-Abl kinase activity. These results must, however, be interpreted cautiously. Increased expression of lineage-specific markers and decreased expression of stem cell markers during the culture period indicate that the initial population and the final population are phenotypically different. It is therefore unclear whether the initial population would likewise demonstrate Bcr-Abl inhibition or whether the cells we observed at the end of the culture period were differentiated to a point where they had become imatinib sensitive. As apoptotic effects of imatinib in cell lines require several days in culture[15], it is not feasible to shorten the culture period, thus *in vitro* culture studies are limited in their ability to provide information about persistent populations.

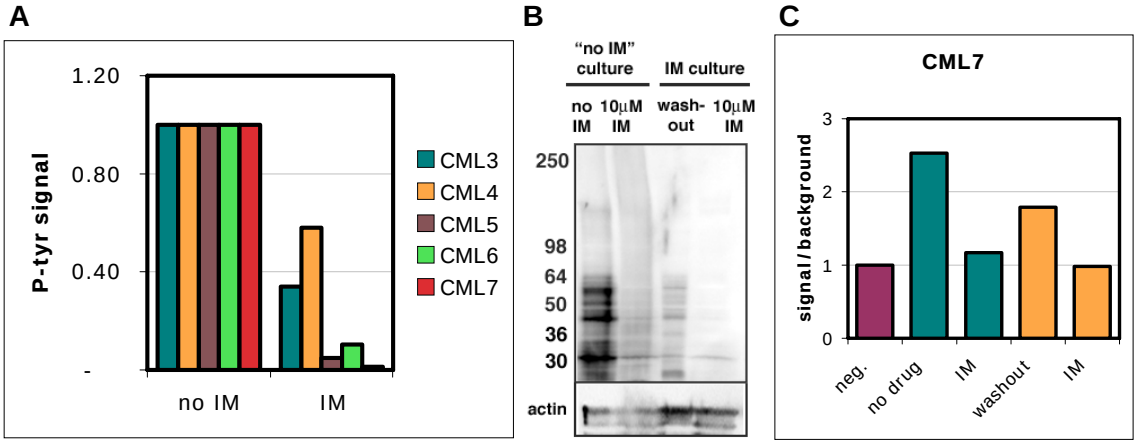

Figure 2. Inhibition of phosphotyrosine in CML Lin- cells cultured with 10mM imatinib. **A)** composite data from western blots and phospho-FACS is shown for five CML samples. **B)** Representative western blot of cells cultured with "no drug" with or without a short incubation of imatinib and cells cultured with imatinib in which imatinib was either left in prior to lysis, or washed out. **C)** Representative phospho-FACS analysis of conditions described for panel B.

<u>Aim 2</u> – Determine which subpopulations of cells are persistently Bcr-Abl+ in imatinib treated CML patients that have achieved CCR

Seeking persistent cells using stem cell enrichment techniques

Because of challenges interpreting *in vitro* culture results, we chose to focus our study on persistent cells in patients who had achieved a complete cytogenetic remission without a molecular remission. Initially, we determined whether enriching stem/progenitor cells would also enrich residual Ph^+ cells as was previously suggested[3]. Bone marrow from CCR patients was lineage depleted and FACS sorted into $CD34^+CD38^-$, $CD34^+CD38^{low}$, $CD34^+CD38^+$ and Lin^+ fractions and analyzed by FISH for the presence of Bcr-Abl. In two samples, 1% Ph^+ cells were seen in the $CD34^+CD38^{low}$ fraction (Table 3), however, this was not sufficient enrichment to pursue this method.

Table 3. Analysis of Bcr-Abl$^+$ cells in stem/progenitor cell fractions of CCR patients.

sample ID	34^+38^- %Ph^+	34^+38^{low} %Ph^+	34^+38^+ %Ph^+	Lin^+ %Ph^+
CCR1	0	-	0	-
CCR2	0	1	0	0
CCR3	0	1	0	0
CCR4	0	0	0	0

Because our study and previous studies demonstrated survival and accumulation of primitive quiescent Bcr-Abl$^+$ cells in the presence of imatinib[12], we additionally analyzed Lin^-G_0 cells from CCR patients. No enrichment of Bcr-Abl$^+$ cells was observed in the primitive quiescent fraction (Table 4). We concluded that methods of stem cell isolation were unlikely to enrich Bcr-Abl positive cells sufficiently for our studies.

Enrichment of Bcr-Abl-expressing cells

We next sought to refine our methods of Bcr-Abl$^+$ cell enrichment by developing Bcr-Abl-specific means of cell separation. We simultaneously initiated multiple approaches, including detection of Bcr-Abl protein, detection of Bcr-Abl mRNA and identification of CML progenitor cell-specific markers.

Table 4. Analysis of Bcr-Abl$^+$ cells in quiescent stem/ progenitor cells of CCR patients.

sample ID	% G_0	%Ph^+ G_0	%Ph^+ "not G_0"
CCR5	65	0	0
CCR6	31	5.7	5.9
CCR7	22	0	0
CCR8	53	0	0
CCR9	60	5.4	0
CCR10	46	0	0

Bcr-Abl junction-specific antibodies

To detect Bcr-Abl protein independently of c-Bcr and c-Abl, we generated antibodies in chickens (Aves Laboratory) specific to the Bcr-Abl junction regions b3a2 and b2a2[16]. Antibody target recognition was validated by immunoprecipitation (Figure 3A) and flow cytometry (Figure 3B). The b3a2 antibody was capable of immunopreciptating Bcr-Abl and demonstrated a statistically significant increase in fluorescence signal by FACS in Bcr-Abl b3a2-expressing cells relative to Bcr-Abl negative and Bcr-Abl b2a2 expressing cells. Specificity was not seen with the b2a2 antibody.

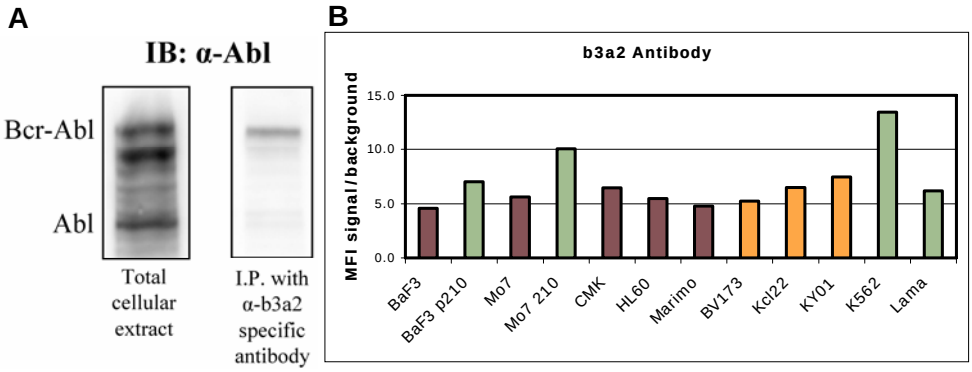

Figure 3. Detection of Bcr-Abl using a b3a2 junction-specific antibody. **A)** Immunoprecipitation of Bcr-Abl with a b3a2 antibody. **B)** Intracellular FACS with a b3a2 antibody in Bcr-Abl negative (purple) b3a2 (green) and b2a2 (orange) Bcr-Abl expressing cells.

K562 cells diluted into Bcr-Abl-negative HL60 cells were sorted based on the b3a2 antibody signal and sorted populations were analyzed by FISH for Bcr-Abl. Enrichment of Bcr-Abl$^+$ cells was seen even in a high background of Bcr-Abl$^-$ cells (Table 5).

Table 5. Enrichment of Bcr-Abl$^+$ cells with a Bcr-Abl b3a2-specific antibody

Dilution	Post Sort b3a2$^-$ %Ph$^+$	Post Sort b3a2$^+$ %Ph$^+$
1:1 K562:HL60	1%	100%
1:100 K562:HL60	0%	72%

CML CD34$^+$ and normal CD34$^+$ bone marrow cells were analyzed by intracellular FACS with the b3a2 antibody. Selective detection of CML cells was observed (Figure 4).

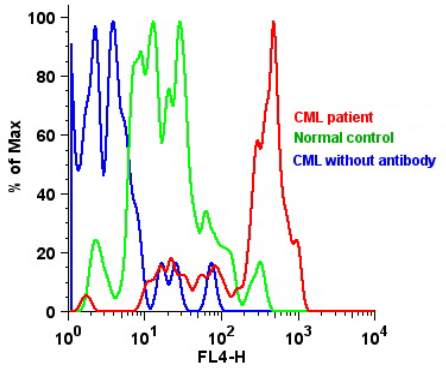

Figure 4. Intracellular FACS analysis of normal (green) and CML (red) CD34+ cells with a b3a2 specific Bcr-Abl antibody.

Future experiments include increasing the number of primary specimens used to test the b3a2 antibody and FACS sorting CML $CD34^+$ cells diluted into a normal background to test the utility of this antibody for selection of CML cells. Because this is a polyclonal antibody, high background staining may obscure weaker differences in signal. To address this issue, we will employ methods of subtractive affinity purification to remove any contaminating antibodies that may bind to c-Bcr or c-Abl. Once specific recognition is reproducibly established, CCR $CD34^+$ cells will be FACS sorted based on b3a2 signal and analyzed for enrichment of $Bcr\text{-}Abl^+$ cells.

Bcr-Abl mRNA hybridization

To specifically detect Bcr-Abl mRNA, we designed a single stranded DNA probe against the Bcr-Abl b3a2 junction. A molecular beacon dye/quencher strategy was used as a method of signal detection[17]. Bcr-Abl specific signal was observed in K562 cells with the molecular beacon relative to a non-specific scrambled probe (Figure 5) however background signal was high, even under optimized hybridization conditions. Addition of a second probe to introduce a dual FRET molecular beacon strategy has been shown to reduce non-specific background[17].

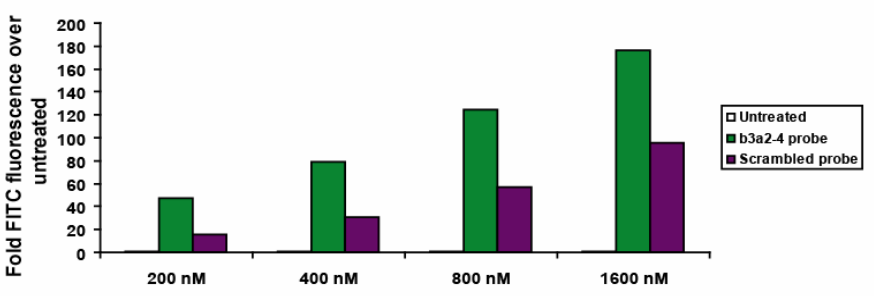

Figure 5. Detection of Bcr-Abl in K562 using a b3a2 junction-specific molecular beacon (green) versus a non-specific scrambled probe (purple).

CML-specific markers

An alternative strategy to isolate CML cells from a normal background is to identify markers that are specific for CML stem and progenitor cells. Literature searches identified CD33[18,19], CD123[19,20] and WT-1[21] as candidate markers that were shown to be upregulated either at the mRNA or protein level in CML versus normal cells. Additionally, we performed a microarray

meta-analysis using publicly available data of gene expression profiles in normal versus CML $CD34^+$ cells[22] as well as CML $CD34^+$ data that we generated in the context of a separate project. Several candidate cell-surface as well as intracellular markers were identified (Table 6).

Table 6. FACS analysis of candidate markers for CML and normal stem/progenitor cells.

gene	mRNA CML/normal	FACS CML/normal	p value
Leptin Receptor	3.9	1.5	0.14
CD29	3.1	1.1	0.23
CD114	0.30	1.3	0.19
CD61	0.23	1.6	0.14
CD54*	0.20	1.3	0.004
CD33	n/a	2.7	0.12
CD123	n/a	1.0	0.50
Prefoldin-4*	10.1	1.5	0.007
Ski*	9.2	1.4	0.03
K-Ras*	6.7	1.3	0.04
RALA	5.4	1.1	0.13
Opioid receptor mu1	4.4	1.1	0.36
Jak2	4.3	1.2	0.14
TRF1	4.3	1.5	0.06
WT-1*	n/a	1.3	0.008
c-Abl/Bcr-Abl*	n/a	1.6	0.00007
c-Bcr/Bcr-Abl	n/a	1.0	0.38

Abl and Bcr expression levels relative to Bcr-Abl were also considered. All candidate markers were analyzed by FACS using cell surface or intracellular staining of CML and normal CD34+ cells. Relative fluorescence intensities of CML/normal were compared (table 6). Representative data for WT-1 is shown (Figure 6).

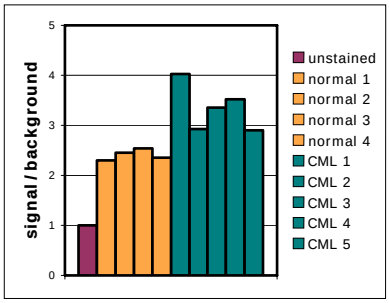

Figure 6. Intracellular FACS analysis of WT-1 expression in normal (orange) and CML (teal) CD34+ cells.

Those demonstrating a statistically different signal between normal and CML (represented by *) all showed <2-fold difference in CML/normal. Additional optimization steps were taken to determine whether the CML-specific signal could be enhanced. Among the difficulties encountered were limited availability of suitable monoclonal antibodies, poor antibody quality,

poor antibody specificity and the need to optimize cell permeabilization techniques for intracellular staining. Western blots of a variety of Bcr-Abl negative and positive cell lines demonstrated that the antibody for prefoldin 4 was unable to recognize its target and available antibodies for K-Ras recognize all of the Ras isoforms. Thus, these targets were discarded. Ski-1 and TRF-1 antibodies both showed specificity for their targets in western blots and by FACS analysis, however, the optimal permeabilization technique for FACS was incompatible with cell surface staining for CD34+ cells. Additional permeabilization techniques are being tested for these antibodies[23].

WT-1 expression and c-Abl/Bcr-Abl expression were used as a means of sorting CML from normal cells. CML and normal $CD34^+$ cells stained with either WT-1 antibody or Abl 24-21 were mixed at equal ratios and sorted based on WT-1 or Abl signal.

Table 7. Enrichment of Bcr-Abl^+ cells in WT-1^{high} and Abl^{high} fractions of mixed normal and CML $CD34^+$ cells.

	Post Sort Ph+
WT-1^{low}	38%
WT-1^{high}	78%
Abl^{low}	25%
Abl^{high}	75%

Sorted cells were analyzed by FISH for Bcr-Abl. Incomplete enrichment was observed for both markers tested (Table 7). Additionally, Abl staining and FACS sorting of $CD34^+$ marrow cells from CML patients who had achieved a partial cytogenetic remission on imatinib did not yield any enrichment of Bcr-Abl^+ cells (data not shown) suggesting that the small differences in signal observed with WT-1 and Abl staining may not be sufficient to achieve the separation necessary for our studies.

In addition to improving staining techniques for candidate markers, additional markers identified by the microarray meta-analysis will be explored with an emphasis on those amenable to cell surface staining.

KEY RESEARCH ACCOMPLISHMENTS

- Analysis of proliferation, cell cycle status, tyrosine phosphorylation and imatinib sensitivity of newly diagnosed CML stem/progenitor cells in an *in vitro* culture system.
- Assessment of the frequency of CML cells among stem cell and quiescent progenitor cell populations of patients in CCR.
- Development of a Bcr-Abl junction-specific antibody capable of distinguishing Bcr-Abl positive and CML cells from normal cells.
- Development of a Bcr-Abl junction-specific molecular beacon capable of distinguishing Bcr-Abl positive cells from Bcr-Abl negative cells.
- Evaluation of seventeen potential markers for CML stem cells.

REPORTABLE OUTCOMES

None to report at this time.

CONCLUSIONS

To address the mechanisms of disease persistence in imatinib-treated CML, we initially studied the *in vitro* effects of imatinib on newly diagnosed CML stem/progenitor cells. We observed inhibition of proliferation of these cells relative to untreated specimens as well as a slight increase in quiescent cells upon imatinib treatment, consistent with previously published data[12]. The presence of cycling cells and the net increase in cell number in the presence of imatinib, however, demonstrates that proliferating cells as well as quiescent cells are capable of surviving imatinib treatment. Additionally, we observed inhibition of Bcr-Abl kinase activity in cells surviving imatinib treatment, suggesting that their proliferation and survival were independent of Bcr-Abl activity. A decrease in stem cell markers during the culture period, however, suggests that differentiation had occurred during the culture period. While we can conclude that in the final cell population Bcr-Abl was inhibited by imatinib, it is impossible to extrapolate this result to the starting cell sample.

Because of this difficulty in interpretation of *in vitro* culture studies, we focused on isolating persistent cells from patients in cytogenetic remission. Enrichment strategies using stem cell markers or the property of quiescence did not enrich the Bcr-Abl$^+$ population, therefore we focused extensively on methods of Bcr-Abl-specific detection. We generated a Bcr-Abl b3a2 junction-specific antibody capable of selectively recognizing Bcr-Abl expressing cell lines and primary CML progenitors by FACS analysis. We additionally developed a Bcr-Abl b3a2 junction-specific molecular beacon capable of selectively detecting Bcr-Abl mRNA in Bcr-Abl expressing cells. Finally, we evaluated CML progenitor cell markers identified by microarray meta-analysis. Additional experiments will focus on larger scale evaluation and optimization of Bcr-Abl detection in primary CML cells and attempts to isolate persistent CML cells from patients in cytogenetic remission.

The majority of studies to date characterizing mechanisms of disease persistence focus on newly diagnosed or untreated CML cells either newly isolated or cultured *in vitro* to identify imatinib-resistant populations. As our studies have shown, results obtained by this method are complicated by culture-induced changes to the cells. Also, it is impossible to assess whether resistant populations identified by *in vitro* culture behave similarly to persistent CML cells in CCR patients. Through the development of sophisticated methods of CML cell isolation, we hope to study mechanisms of imatinib persistence in pertinent cell populations. This approach will be critical for a thorough understanding of disease persistence and may allow identification of novel drug targets or methods to sensitize resistant cells to imatinib or alternative Bcr-Abl kinase inhibitors.

REFERENCES

1. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2003;348:994-1004.
2. Hughes TP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. N Engl J Med. 2003;349:1423-1432.
3. Bhatia R, Holtz M, Niu N, et al. Persistence of malignant hematopoietic progenitors in chronic myelogenous leukemia patients in complete cytogenetic remission following imatinib mesylate treatment. Blood. 2003;101:4701-4707.
4. Zhou S, Schuetz JD, Bunting KD, et al. The ABC transporter Bcrp1/ABCG2 is expressed in a wide variety of stem cells and is a molecular determinant of the side-population phenotype. Nat Med. 2001;7:1028-1034.
5. Chaudhary PM, Roninson IB. Expression and activity of P-glycoprotein, a multidrug efflux pump, in human hematopoietic stem cells. Cell. 1991;66:85-94.
6. Burger H, van Tol H, Boersma AW, et al. Imatinib mesylate (STI571) is a substrate for the breast cancer resistance protein (BCRP)/ABCG2 drug pump. Blood. 2004;104:2940-2942.
7. Illmer T, Schaich M, Platzbecker U, et al. P-glycoprotein-mediated drug efflux is a resistance mechanism of chronic myelogenous leukemia cells to treatment with imatinib mesylate. Leukemia. 2004;18:401-408.
8. Mahon FX, Belloc F, Lagarde V, et al. MDR1 gene overexpression confers resistance to imatinib mesylate in leukemia cell line models. Blood. 2003;101:2368-2373.
9. Deininger M, Buchdunger E, Druker BJ. The development of imatinib as a therapeutic agent for chronic myeloid leukemia. Blood. 2005;105:2640-2653.
10. Xiaoyan J, Zhao Y, Chan WY, Pang E, Eaves A, Eaves C. Leukemic stem cells of chronic phase CML patients consistently display very high BCR-ABL transcript levels and reduced responsiveness to imatinib mesylate in addition to generating a rare subset that produce imatinib mesylate resistant differentiated progeny. Blood. 2004;104:Abstract #711.
11. Holyoake T, Jiang X, Eaves C, Eaves A. Isolation of a highly quiescent subpopulation of primitive leukemic cells in chronic myeloid leukemia. Blood. 1999;94:2056-2064.
12. Graham SM, Jorgensen HG, Allan E, et al. Primitive, quiescent, Philadelphia-positive stem cells from patients with chronic myeloid leukemia are insensitive to STI571 in vitro. Blood. 2002;99:319-325.
13. Rizo A, Vellenga E, de Haan G, Schuringa JJ. Signaling pathways in self-renewing hematopoietic and leukemic stem cells: do all stem cells need a niche? Hum Mol Genet. 2006;15 Spec No 2:R210-219.
14. Holyoake TL, Jiang X, Jorgensen HG, et al. Primitive quiescent leukemic cells from patients with chronic myeloid leukemia spontaneously initiate factor-independent growth in vitro in association with up-regulation of expression of interleukin-3. Blood. 2001;97:720-728.
15. La Rosee P, Shen L, Stoffregen EP, Deininger M, Druker BJ. No correlation between the proliferative status of Bcr-Abl positive cell lines and the proapoptotic activity of imatinib mesylate (Gleevec/Glivec). Hematol J. 2003;4:413-419.
16. Deininger MW, Goldman JM, Melo JV. The molecular biology of chronic myeloid leukemia. Blood. 2000;96:3343-3356.
17. Santangelo P, Nitin N, Bao G. Nanostructured probes for RNA detection in living cells. Ann Biomed Eng. 2006;34:39-50.
18. Jilani I, Estey E, Huh Y, et al. Differences in CD33 intensity between various myeloid neoplasms. Am J Clin Pathol. 2002;118:560-566.

19. Florian S, Sonneck K, Hauswirth AW, et al. Detection of molecular targets on the surface of CD34+/CD38-- stem cells in various myeloid malignancies. Leuk Lymphoma. 2006;47:207-222.
20. Jordan CT, Upchurch D, Szilvassy SJ, et al. The interleukin-3 receptor alpha chain is a unique marker for human acute myelogenous leukemia stem cells. Leukemia. 2000;14:1777-1784.
21. Gao L, Bellantuono I, Elsasser A, et al. Selective elimination of leukemic CD34(+) progenitor cells by cytotoxic T lymphocytes specific for WT1. Blood. 2000;95:2198-2203.
22. Kronenwett R, Butterweck U, Steidl U, et al. Distinct molecular phenotype of malignant CD34(+) hematopoietic stem and progenitor cells in chronic myelogenous leukemia. Oncogene. 2005;24:5313-5324.
23. Krutzik PO, Nolan GP. Intracellular phospho-protein staining techniques for flow cytometry: monitoring single cell signaling events. Cytometry A. 2003;55:61-70.

APPENDIX

CVs

- Brian Druker, MD – Principal Investigator
- Amie Corbin, BA – Research Associate

BRIAN J. DRUKER

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Born: April 30, 1955 – St. Paul, Minnesota

EDUCATION

B.A., University of California, San Diego, CA	1977
M.D., University of California School of Medicine, San Diego, CA	1981

POSTDOCTORAL TRAINING

Internship and Residency in Internal Medicine	1981-1984
Barnes Hospital, Washington University School of Medicine, St. Louis, MO	
Fellowship in Medical Oncology	1984-1987
Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA	

ACADEMIC APPOINTMENTS

Instructor in Medicine	1987-1993
Harvard Medical School, Boston, MA	
Associate Professor	1993-2000
Department of Medicine, Oregon Health & Science University (OHSU)	
Joint Appointment	1993-present
Department of Cell and Developmental Biology, OHSU	
Program Leader	1993-present
Hematologic Malignancies, OHSU Cancer Institute	
Joint Appointment	1996-present
Department of Biochemistry and Molecular Biology, OHSU	
Director / Associate Director	1996-2002
OHSU MD/PhD Program	
Professor of Medicine	2000-present
Division of Hematology & Medical Oncology, OHSU	
Investigator	2002-present
Howard Hughes Medical Institute	

HOSPITAL APPOINTMENTS

Clinical Associate	1987-1993
Dana-Farber Cancer Institute, Boston, MA	
Associate Physician	1987-1993
Brigham and Women's Hospital, Boston, MA	
Medical Director	1987-1993
Nashoba Community Hospital, Oncology Clinic, Ayer, MA	
Staff Physician	1993
University Hospital and Clinics, OHSU	
Co-Director	1993-present
Center for Hematologic Malignancies, OHSU Cancer Institute	

AWARDS AND HONORS

President's Undergraduate Research Award - University of California, San Diego	1976
Phi Beta Kappa	1977
B.A. Summa Cum Laude, University of California, San Diego	1977
American Society for Clinical Investigation	1997
Teaching Award, OHSU 2nd Year Medical School Class	1998
Discovery Award, Oregon Health Sciences Foundation	1999
Lifetime Achievement Award, The Leukemia and Lymphoma Society, Washington Chapter	2000
Translational Research Award, Burroughs Wellcome Fund	2000
Outstanding Alumnus, University of California, San Diego	2000
Distinguished Faculty Award for Outstanding Research, OHSU Foundation & Faculty Senate	2000
John J. Kenny Award, The Leukemia and Lymphoma Society	2000
Charles Rodolphe Brupbacher Prize for Cancer Research	2001
AACR-Richard and Hinda Rosenthal Foundation Award	2001
Emil J. Freireich Award, The University of Texas MD Anderson Cancer Center	2001
Warren Alpert Foundation Prize, Harvard Medical School	2001
Dameshek Prize, The American Society of Hematology	2001
JELD-WEN Chair of Leukemia Research, JELD-WEN, Klamath Falls, Oregon	2001
Donald Ware Waddell Award Lecture, Arizona Cancer Center	2002
Alexandra J. Kefalides Prize for Leukemia Research, University of Pennsylvania Cancer Center	2002
Pioneer of Survivorship Carpe Diem Award, Lance Armstrong Foundation	2002
Medal of Honor, American Cancer Society	2002
Charles F. Kettering Prize, General Motors Cancer Research Foundation	2002
City of Medicine Award, Durham Health Partners, Inc.	2002
Novartis-Drew University Award in Biomedical Research	2002
International Citizen Award, Oregon Consular Corps	2002
Days of Molecular Medicine Translational Medicine Award, UC San Diego-Nature Medicine	2003
David A. Karnofsky Award, American Society of Clinical Oncology	2003
Braunschweig Preis, City of Braunschweig	2003
Member, Institute of Medicine: National Academy of Sciences	2003
Humanitarian Award, The Life Raft Group	2004
Outstanding Program Award, Center for Diversity and Multicultural Affairs, OHSU	2004
Commercialization Award, OHSU	2004
Dr. Alvin J. Thompson Award, Northwest Association for Biomedical Research	2004
Doctor of Science, Honorary Degree, State University of New York	2004
Naomi M. Kanof Clinical Investigator Award, The Society for Investigative Dermatology	2004
Alpha Omega Alpha	2004
David Nathans Memorial Award, Van Andel Institute	2005
Biotech Hall of Fame Award for Scientific Achievement, The Biotech Meeting	2005
Robert-Koch Prize, Robert Koch Foundation	2005
Technology Innovation Award, OHSU	2005
STAR Medical Research Award, Angel Foundation	2006
Member, American Association of Physicians	2006
Technology Innovation Award, OHSU	2006
Golden Plate Award, Academy of Achievement	pending 2007

LICENSURE AND CERTIFICATION

Diplomate, National Board of Medical Examiners	1982
Massachusetts License Registration No. 52706	1984-1993
American Board of Internal Medicine	1985
American Board of Internal Medicine, Medical Oncology	1987
Oregon Board of Medical Examiners No. 18379	1993

PROFESSIONAL AFFILIATIONS

American Association for the Advancement of Science (AAAS)
American Society of Hematology (ASH)
American Society for Microbiology (ASM)
American Society for Clinical Investigation (ASCI)
American Society of Clinical Oncology (ASCO)
American Association for Cancer Research (AACR)
Children's Oncology Group (COG)
The American Society for Cell Biology (ASCB)

MAJOR RESEARCH INTERESTS

- Identification and characterization of substrates of activated tyrosine kinases with specific emphasis on the BCR-ABL tyrosine kinase
- Evaluation of specific ABL tyrosine kinase inhibitors as mechanism based therapeutic agents for chronic myelogenous leukemia
- Identification of molecular pathogenetic events in leukemia with specific emphasis on tyrosine kinases and development of inhibitors of these kinases
- Clinical trials of molecularly targeted agents

TEACHING RESPONSIBILITIES AT OHSU

Lecturer, CON 654: Topics in Signal Transduction, Graduate	1993-present
Lab Instructor/Lecturer, MSCI 623: Pathophysiology of Blood, 2nd year Medical	1994-present
Lab Instructor, BBOD: Biology of Neoplasia, 1st year Medical	1994-present
Lecturer, CELL 616: Cancer Biology, Graduate	1994-present
Lecturer, CON 653: Molecular & Cell Biology II Eukaryotic Cell Biology, Graduate	1995-present
Lecturer, Fellows Training Course	1997-present
Lecturer, HIP 514: Molecular Biology for Clinical Research, Continuing	2005-present
Lecturer, CON 665: Development, Differentiation and Cancer, Graduate	2005-present

GRANT REVIEW

American Society of Hematology, Fellow and Junior Scholar Awards	1997
Damon Runyon-Lilly Clinical Investigator Award Committee	2003-2005
Department of Defense Chronic Myelogenous Leukemia Research Program, Ad Hoc Reviewer	2004
Doris Duke Charitable Foundation, Clinical Scientist Development Award, Reviewer	2001-2005
Fanconi Anemia Research Fund	1996, 1997
Israel Science Foundation, Ad Hoc Reviewer	2000
National Institutes of Health (NIH)	
Hematology Study Section I, Ad Hoc Reviewer	1995, 1996
Hematology Study Section I, Permanent Member	1997-2001
M.D. Anderson Cancer Center, CML Program Project Grant	1994
National Cancer Institute (NCI)	
▪ Cold Spring Harbor Cancer Center Grant	1995
▪ Thomas Jefferson University, Cancer Center Grant	1994, 1998
National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK)	
▪ Centers of Excellence, Molecular Hematology	1994
Oncological Sciences, Special Emphasis Panel, Myeloid Leukemia	2005
XVII International Symposium for Comparative Research on Leukemia and Related Diseases	1994
United States-Israel Binational Science Foundation, Ad Hoc Reviewer	1996
VA Merit Award, Ad Hoc Reviewer	1995, 1996, 1997

MANUSCRIPT REVIEW & EDITORIAL RESPONSIBILITIES

Editorial Board, Blood	1998-2002
Editorial Board, Cancer Cell	2001-present
Editorial Board, Cell Cycle	2002-present
Senior Editor, Molecular Cancer Therapeutics	2003-present
Senior Editor, Hematologic Malignancies, Hem/Onc Today	2005-present
Editorial Advisory Board, Handbook of Genomic Medicine	2005-present
Associate Editor, Blood	2006-present

Ad hoc reviewer: British Journal of Haematology • Cancer Research • Clinical Cancer Research • Experimental Hematology • Journal of Biological Chemistry • Journal of Clinical Investigation • Journal of Clinical Oncology • Journal of the American Medical Association • The New England Journal of Medicine • Proceedings of the National Academy of Science

COMMITTEE & BOARD MEMBERSHIP

American Association for Cancer Research	
Board of Directors	2002-2005
Clinical and Experimental Therapeutic Awards, Selection Committee	2003-2004
2005 Pezcoller Foundation-AACR International Award for Cancer Research Selection Committee	2004
Clinical Research and Experimental Therapeutics Awards, Nominating Committee	2004-2005
2005 Award for Lifetime Achievement in Cancer Research, Selection Committee	2004-2005
2006 Pezcoller Foundation-AACR International Award for Cancer Research, Nominating Committee	2005
American Society of Clinical Oncology, Program Committee Member: Adult Leukemia & Lymphoma	2001-2002
American Society of Hematology, Scientific Committee on Neoplasia	2000-2004
American Medical Informatics Association: Global Trial Bank, Steering Committee	2005-present
Institute of Medicine, Cancer and Cancer Biology Interest Group	2005-present
The Leukemia & Lymphoma Society	
Oregon Chapter Board of Trustees	1993-2003
National Board of Trustees	2002-2003
▪ Medical and Scientific Affairs Committee	2001-present
- Professional Education Subcommittee	2004-present
▪ Brand Communications Committee	2002-2004
Concert/Collaborations Resource Team	2006-present
Research Foundation	2006-present
Co-Chair, Search Committee for Executive Vice President	2006
The Max Foundation, Scientific Medical Board	2002-present
Multiple Myeloma Research Consortium, External Advisory Board	2004-present
National Cancer Institute	
Molecular Targets Working Group, Organ Systems Branch	2003-2004
Advanced Biomedical Technology Development Working Group, National Cancer Advisory Board (Chair, Cancer Therapeutics Focus Group)	2003-2005
External Scientific Committee, NHGRI Human Cancer Genome Project	2005-present
▪ Ethics, Law, & Policy Subcommittee	2005-present
National Institutes of Health, Advisory Committee to the Director: Working Group on the Protection of the Taxpayers' Interests	2003-2004

Oregon Health & Science University	
Senior Leadership Council, OHSU Cancer Institute	1993-present
▪ Executive Committee	1993-present
Search Committee, Endowed Chair – Cancer Research	1994-1995
Institutional Review Board	1994-1997
Heme/Onc Fellowship Task Force	1995
Department of Medicine Task Force for Faculty Productivity	1995
Internal Advisory Board, Center for the Study of Weight Regulation	2003-present
Internal Advisory Board, Stem Cell Biology Center	2004-present
Research Council	2004-2006
Research Steering Plan Committee	2006-present
Research Strategic Plan Committee	1998-1999
Founding Member, Oregon Clinical and Translational Science Institute (OCTSI)	2006-present
Public Library of Science (PLoS), Board of Directors	2003-present
Southwest Oncology Group, Leukemia Committee	2006-present
▪ Leukemia Translational Medicine Subcommittee	2006-present
University of California San Diego, Rebecca and John Moores UCSD Cancer Center	
External Scientific Advisory Board	2004-present
University of Minnesota Cancer Center and School of Pharmacy,	
Experimental Therapeutics Scientific Advisory Committee	2004-present

BIBLIOGRAPHY

Original Publications

1. Wepsic HT, Alaimo J, Druker BJ, Murray W IV, Morris HP. The negative systemic effect of BCGcw inoculated intraperitoneally. I. In vivo demonstration of intramuscular tumor growth enhancement using Morris hepatomas. *Cancer Immunol Immunother* 10:217-225, 1981.
2. Druker BJ, Wepsic HT, Alaimo J, Murray W IV. The negative systemic effect of BCGcw inoculated intraperitoneally. II. The in vitro demonstration of the presence of suppressor cells in BCGcw immunized rats. *Cancer Immunol Immunother* 10:227-237, 1981.
3. Druker BJ, Wepsic HT, Alaimo JC, Murray W IV, Vranes AJ. Identification and characterization of the BCG cell wall-stimulated suppressor cells in inbred rats. *Intl J Oncodevel Biol Med* 3:209-221, 1982.
4. Druker BJ and Wepsic HT. Identification and characterization of the BCG. *Cancer Invest* 1:151-161, 1983.
5. Draetta G, Piwnica-Worms H, Morrison D, Druker B, Roberts T, Beach D. Human cdc2 protein kinase is a major cell-cycle regulated tyrosine kinase substrate. *Nature* 336:738-744, 1988.
6. Druker BJ, Rosenthal DR, Canellos GP. Chlorambucil, vinblastine, procarbazine and prednisone: an effective but less toxic regimen than MOPP for advanced-stage Hodgkin's disease. *Cancer* 63:1060-1064, 1989.
7. Druker BJ, Mamon HJ, Roberts TM. Oncogenes, growth factors and signal transduction. *N Engl J Med* 321:1383-1391, 1989.
8. Varticovski L, Druker B, Morrison D, Cantley L, Roberts T. The colony stimulating factor-1 receptor associates with and activates phosphatidylinositol-3 kinase. *Nature* 342:699-702, 1989.
9. Druker BJ, Ling LE, Cohen B, Roberts TM, Schaffhausen BS. A completely transformation-defective point mutant of polyomavirus middle T antigen which retains full associated phosphatidylinositol kinase activity. *J Virol* 64:4454-61, 1990.
10. Cohen B, Liu Y, Druker B, Roberts TM, Schaffhausen BS. Characterization of pp85, a target of oncogenes and growth factor receptors. *Mol Cell Biol* 10:2909-2915, 1990.

11. Epstein RJ, Druker BJ, Roberts TM, Stiles CD. Modulation of a 175,000 M_r c-neu receptor isoform in G8/DHFR cells by serum starvation. *J Biol Chem* 265:10746-10751, 1990.
12. Kanakura Y, Druker B, Cannistra SA, Furukawa Y, Torimoto Y, Griffin JD. Signal transduction of the human granulocyte-macrophage colony-stimulating factor and interleukin-3 receptors involves tyrosine phosphorylation of a common set of cytoplasmic proteins. *Blood* 76:706-715, 1990.
13. Kanakura Y, Druker B, Wood KW, Mamon HJ, Okuda K, Roberts TM, Griffin JD. Granulocyte-macrophage colony-stimulating factor and interleukin-3 induce rapid phosphorylation and activation of the proto-oncogene raf-1 in a human factor-dependent myeloid cell line. *Blood* 77:243-248, 1991.
14. Kanakura Y, Druker B, DiCarlo J, Cannistra SA, Griffin JD. Phorbol 12-myristate 13-acetate inhibits granulocyte-macrophage colony stimulating factor-induced protein tyrosine phosphorylation in a human factor-dependent hematopoietic cell line. *J Biol Chem* 266:490-495, 1991.
15. Vivier E, Morin P, O'Brien C, Druker B, Schlossman SF, Anderson P. Tyrosine phosphorylation of the FcγRIII (CD16): ζ complex expressed by human natural killer cells. *J Immunol* 146:206-210, 1991.
16. Burgess KE, Odysseos AD, Zalvan C, Druker BJ, Anderson P, Schlossman SF, Rudd CE. Biochemical identification of a direct physical interaction between the CD4:$p56^{lck}$ and T_i(TcR)/CD3 complexes. *Eur J Immunol* 21:1663-1668, 1991.
17. Longnecker R, Druker B, Roberts TM, Kieff E. An Epstein-Barr virus protein associated with cell growth transformation interacts with a tyrosine kinase. *J Virol* 65:3681-3692, 1991.
18. Davis S, Lu ML, Lo SH, Lin S, Butler JA, Druker BJ, Roberts TM, An Q, Chen LB. Presence of an Sh2 domain in the actin-binding protein tensin. *Science* 252:712-715, 1991.
19. Ley SC, Davies AA, Druker B, Crumpton MJ. The T cell receptor/CD3 complex and CD2 stimulate the tyrosine phosphorylation of indistinguishable patterns of polypeptides in the human T leukemia cell line Jurkat. *Eur J Immunol* 21:2203-2209, 1991.
20. Okuda K, Druker B, Kanakura Y, Koenigsman M, Griffin JD. Internalization of the granulocyte-macrophage colony-stimulating factor receptor is not required for induction of protein tyrosine-phosphorylation in human myeloid cells. *Blood* 78:1928-1935, 1991.
21. Kuriu A, Ikeda A, Kanakura Y, Griffin JD, Druker B, Yagura H, Kitayama H, Ishikawa J, Nishiura T, Kanayama Y, Yonezawa T, Tarui S. Proliferation of human myeloid leukemia cell line associated with the tyrosine phosphorylation and activation of the proto-oncogene c-kit product. *Blood* 78:2834-2840, 1991.
22. Druker BJ and Roberts TM. Generation of a large library of point mutations in polyoma middle T antigen. *Nucl Acids Res* 19:6855-6861, 1991.
23. Held JL, Druker BJ, Kohn SR, Byrnes W, Margolis RJ. Atypical, nonfatal, transfusion-associated, acute graft-versus-host disease in a patient with Hodgkin's disease. *J Am Acad Dermatol* 26:261-262, 1992.
24. Tamaki T, Kanakura Y, Kuriu A, Ikeda H, Mitsui H, Yagura H, Matsumura I, Druker B, Griffin JD, Kanayama Y, Yonezawa T. Surface immunoglobulin-mediated signal transduction involves rapid phosphorylation and activation of the protooncogene product Raf-1 in human B-cells. *Cancer Res* 52:566-570, 1992.
25. Dasgupta JD, Granja C, Druker B, Lin L-L, Yunis EJ, Relias V. Phospholipase C-γ1 association with CD3 structure in T cells. *J Exp Med* 175:285-288, 1992.
26. Ling LE, Druker BJ, Cantley LC, Roberts TM. Transformation-defective mutants of polyoma-virus middle T antigen associate with phosphatidylinositol 3-kinase (PI 3-kinase) but are unable to maintain wild-type levels of PI 3-kinase products in intact cells. *J Virol* 66:1702-1708, 1992.

27. Oda A, Druker BJ, Smith M, Salzman EW. Inhibition by sodium nitroprusside or PGE_1 of tyrosine phosphorylation induced in platelets by thrombin or ADP. *Am J Physiology* 262:701-707, 1992.
28. Bachelot C, Cano E, Grelac F, Saleun S, Druker BJ, Levy-Toledano S, Fischer S, Rendu F. Functional implications of tyrosine protein phosphorylation in platelets: simultaneous studies with different agonists and inhibitors. *Biochem J* 284:923-928, 1992.
29. Epstein R, Druker BJ, Irminger J-C, Jones SD, Roberts TM, Stiles CD. Extracellular calcium mimics the actions of platelet-derived growth factor on mouse fibroblasts. *Cell Growth and Differentiation* 3:157-164, 1992.
30. Okuda K, Sanghera JS, Pelech SL, Kanakura Y, Hallek M, Griffin JD, Druker BJ. Granulocyte-macrophage colony-stimulating factor, interleukin-3, and steel factor induce rapid tyrosine phosphorylation of p42 and p44 MAP kinase. *Blood* 79:2880-2887, 1992.
31. Druker BJ, Sibert L, Roberts TM. Polyomavirus middle T-antigen NPTY mutants. *J Virol* 66:5770-5776, 1992.
32. Druker B, Okuda K, Matulonis U, Salgia R, Roberts T, Griffin JD. Tyrosine phosphorylation of rasGAP and associated proteins in chronic myelogenous leukemia cell lines. *Blood* 79:2215-2220, 1992.
33. Epstein RJ, Druker BJ, Roberts TM, Stiles CD. Synthetic phosphopeptide immunogens yield activation-specific antibodies to the c-erbB-2 receptor. *Proc Natl Acad Sci USA* 89:10435-10439, 1992.
34. Hallek M, Druker B, Lepisto EM, Wood KW, Ernst TJ, Griffin JD. Granulocyte-macrophage colony-stimulating factor and steel factor induce phosphorylation of both unique and overlapping signal transduction intermediates in a human factor-dependent hematopoietic cell line. *J Cell Physiol* 153:176-186, 1992.
35. Oda A, Druker, BJ, Smith M, Salzman EW. Association of pp60src with Triton X-100-insoluble residue in human blood platelets requires platelet aggregation and actin polymerization. *J Biol Chem* 267:20075-20081, 1992.
36. Egerton M, Burgess WH, Chen D, Druker BJ, Bretscher A, Samelson LE. Identification of ezrin as an 81-kDa tyrosine-phosphorylated protein in T cells. *J Immunol* 149:1847-1852, 1992.
37. Egerton M, Ashe OR, Chen D, Druker BJ, Burgess WH, Samelson LE. VCP, the mammalian homologue of cdc48, is tyrosine phosphorylated in response to T cell antigen receptor activation. *EMBO J* 11:3533-3540, 1992.
38. Showers MO, Moreau JF, Linnekin D, Druker B, D'Andrea AD. Activation of the erythropoietin receptor by the Friend spleen focus-forming virus gp55 glycoprotein induces constitutive protein tyrosine phosphorylation. *Blood* 80:3070-3078, 1992.
39. Matulonis U, Salgia R, Okuda K, Druker B, Griffin JD. Interleukin-3 and p210 BCR/ABL activates both unique and overlapping pathways of signal transduction in a factor-dependent myeloid cell line. *Exp Hematol* 21:1460-1466, 1993.
40. Oda A, Druker BJ, Ariyoshi H, Smith M, Salzman EW. pp60src is an endogenous substrate for calpain in human blood platelets. *J Biol Chem* 268:12603-12608, 1993.
41. Mayeux P, Dusanter-Fourt I, Muller O, Mauduit P, Sabbah M, Druker B, Vainchenker W, Fischer S, Lacombe C, Gisselbrecht S. Erythropoietin induces the association of phosphatidylinositol 3'-kinase with a tyrosine-phosphorylated protein complex containing the erythropoietin receptor. *Eur J Biochem* 216:821-828, 1993.
42. Weiss M, Yokoyama C, Shikama Y, Naugle C, Druker B, Seiff CA. Human granulocyte-macrophage colony-stimulating factor receptor signal transduction requires the proximal cytoplasmic domains of the αand β subunits. *Blood* 82:3298-3306, 1993.

43. Carlesso N, Griffin JD, Druker BJ. Use of a temperature-sensitive mutant to define the biological effects of the $p210^{BCR-ABL}$ tyrosine kinase on proliferation of a factor-dependent murine myeloid cell line. *Oncogene* 9:149-156, 1994.

44. Matsuguchi T, Salgia R, Hallek M, Eder M, Druker B, Ernst TJ, Griffin JD. Shc phosphorylation in myeloid cells is regulated by granulocyte macrophage colony-stimulating factor, interleukin-3, and steel factor and is constitutively increased by $p210^{BCR/ABL}$. *J Biol Chem* 269:5016-5021, 1994.

45. Druker BJ, Neumann M, Okuda K, Franza BR Jr., Griffin JD. rel is rapidly tyrosine-phosphorylated following granulocyte-colony stimulating factor treatment of human neutrophils. *J Biol Chem* 269:5387-5390, 1994.

46. Ley SC, Verbi W, Pappin DJC, Druker B, Davies AA, Crumpton MJ. Tyrosine phosphorylation of αtubulin in human T lymphocytes. *Eur J Immunol* 24:99-106, 1994.

47. Reedquist KA, Fukazawa T, Druker B, Panchamoorthy G, Shoelson SE, Band H. Rapid T-cell receptor-mediated tyrosine phosphorylation of p120, a novel Fyn/Lck Src homology 3 domain-binding protein. *Proc Natl Acad Sci USA* 91:4135-4139, 1994.

48. Campbell KS, Orgis E, Burke B, Su W, Auger KR, Druker BJ, Schaffhausen BS, Roberts TM, Pallas DC. Polyoma middle tumor antigen interacts with SHC protein via the NPTY (Asn-Pro-Thr-Tyr) motif in middle tumor antigen. *Proc Natl Acad Sci USA* 91:6344-6348, 1994.

49. Ramos-Morales F, Druker BJ, Fischer S. Vav binds to several SH2/SH3 containing proteins in activated lymphocytes. *Oncogene* 9:1917-1923, 1994.

50. Dusanter-Fourt I, Muller O, Ziemiecki A, Mayeux P, Druker B, Djiane J, Wilks A, Harpur AG, Fischer S, Gisselbrecht S. Identification of JAK protein tyrosine kinases as signaling molecules for prolactin. Functional analysis of prolactin receptor and prolactin-erythropoietin receptor chimera expressed in lymphoid cells. *EMBO J* 13:2583-2591, 1994.

51. Avalos BR, Broudy VC, Ceselski SK, Druker BJ, Griffin JD, Hammond WP. Abnormal response to granulocyte caused colony-stimulating factor (G-CSF) in canine cyclic hematopoiesis is not caused by altered G-CSF receptor expression. *Blood* 84:789-794, 1994.

52. Oda T, Heaney C, Hagopian JR, Okuda K, Griffin JD, Druker BJ. Crkl is the major tyrosine-phosphorylated protein in neutrophils from patients with chronic myelogenous leukemia. *J Biol Chem* 269:22925-22928, 1994.

53. Okuda K, Matulonis U, Salgia R, Kanakura Y, Druker B, Griffin JD. Factor independence of human myeloid leukemia cell lines is associated with increased phosphorylation of the proto-oncogene Raf-1. *Exp Hematol* 22:1111-1117, 1994.

54. Oda T, Tamura S, Matsuguchi T, Griffin JD, Druker BJ. The SH2 domain of ABL is not required for factor-independent growth induced by BCR-ABL in a murine myeloid cell line. *Leukemia* 9:295-301, 1995.

55. Oda A, Druker BJ, Ariyoshi H, Smith M, Salzman EW. TMB-8 and dibucaine induce tyrosine phosphorylation and dephosphorylation of a common set of proteins in platelets. *Am J Physiol* 269:C118-C125, 1995.

56. Matsuguchi T, Inhorn RC, Carlesso N, Xu G, Druker B, Griffin JD. Tyrosine phosphorylation of $p95^{Vav}$ in myeloid cells is regulated by GM-CSF, IL-3 and steel factor and is constitutively increased by $p210^{BCR/ABL}$. *EMBO J* 14:257-265, 1995.

57. Avalos BR, Hunter MG, Parker JM, Ceselski SK, Druker BJ, Corey SJ, Mehta VB. Point mutations in the conserved box 1 region inactivate the human granulocyte colony-stimulating factor receptor for growth signal transduction and tyrosine phosphorylation of $p75^{c-rel}$. *Blood* 85:3117-3126, 1995.

58. Miyakawa Y, Oda A, Druker BJ, Kato T, Miyazaki H, Handa M, Ikeda Y. Recombinant thrombopoietin induces rapid protein tyrosine phosphorylation of Janus kinase 2 and Shc in human blood platelets. *Blood* 86:23-27, 1995.

59. Fukazawa T, Reedquist KA, Trub T, Soltoff S, Panchamoorthy G, Druker B, Cantley L, Shoelson SE, Band H. The SH3 domain-binding T cell tyrosyl phosphoprotein p120: demonstration of its identity with the c-cbl protooncogene product and in vivo complexes with Fyn, Grb2 and phosphatidylinositol 3-kinase. *J Biol Chem* 270:19141-19150, 1995.

60. Wendtner C-M, Schmitt B, Gruss H-J, Druker BJ, Emmerich B, Goodwin RG, Hallek M. CD30 ligand signal transduction involves activation of a tyrosine kinase and of mitogen-activated protein kinase in a Hodgkin's lymphoma cell line. *Cancer Res* 55:4157-4161, 1995.

61. Fukazawa T, Reedquist KA, Panchamoorthy G, Soltoff S, Trub T, Druker B, Cantley L, Shoelson SE, Band H. T cell activation-dependent association between the p85 subunit of the phosphatidylinositol 3-kinase and Grb2/phospholipase C-γ1-binding phosphotyrosyl protein p36/38. *J Biol Chem* 270:20177-20182, 1995.

62. Pignata C, Prasad KVS, Hallek M, Druker B, Rudd CE, Robertson MJ, Ritz J. Phosphorylation of src family lck tyrosine kinase following interleukin-12 activation of human natural killer cells. *Cellular Immunology* 165:211-216, 1995.

63. Salgia R, Uemura N, Okuda K, Li J-L, Pisick E, Sattler M, de Jong R, Druker B, Heisterkamp N, Chen LB, Groffen J, Griffin JD. CRKL links $p210^{BCR/ABL}$ with paxillin in chronic myelogenous leukemia cells. *J Biol Chem* 270:29145-29150, 1995.

64. Miyakawa Y, Oda A, Druker BJ, Miyazaki H, Handa M, Ohashi H, Ikeda Y. Thrombopoietin induces tyrosine phosphorylation of Stat3 and Stat5 in human blood platelets. *Blood* 87:439-446, 1996.

65. Buchdunger E, Zimmermann J, Mett H, Meyer T, Müller M, Druker BJ, Lydon NB. Inhibition of the Abl protein-tyrosine kinase in vitro and in vivo by a 2-phenylaminopyrimidine derivative. *Cancer Res* 56:100-104, 1996.

66. Panchamoorthy G, Fukazawa T, Miyake S, Soltoff S, Reedquist K, Druker B, Shoelson S, Cantley L, Band H. $p120^{cbl}$ is a major substrate of tyrosine phosphorylation upon B cell antigen receptor stimulation and interacts in vivo with Fyn and Syk tyrosine kinases, Grb2 and Shc adaptors, and the p85 subunit of phosphatidylinositol 3-kinase. *J Biol Chem* 271:3187-3194, 1996.

67. Reedquist KA, Fukazawa T, Panchamoorthy G, Langdon WY, Shoelson SE, Druker BJ, Band H. Stimulation through the T cell receptor induces Cbl association with Crk proteins and the guanine nucleotide exchange protein C3G. *J Biol Chem* 271:8435-8442, 1996.

68. Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, Zimmermann J, Lydon NB. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. *Nature Medicine* 2:561-566, 1996.

69. Oda A, Miyakawa Y, Druker BJ, Ozaki K, Yabusaki K, Shirasawa Y, Handa M, Kato T, Miyazaki H, Shimosaka A, Ikeda Y. Thrombopoietin primes human platelet aggregation induced by shear stress and by multiple agonists. *Blood* 87:4664-4670, 1996.

70. Royal I, Raptis L, Druker BJ, Marceau N. Down-regulation of cytokeratin 14 gene expression by the polyoma virus middle T antigen is dependent on c-Src association but independent of full transformation in rat liver nonparenchymal epithelial cells. *Cell Growth & Differentiation* 7:737-743, 1996.

71. Neumann M, Wilisch A, Ma B-C, Druker BJ, Serfling E, Franza BR Jr. BCR/ABL modulates the cytokine and retinoic acid response of c-Rel in human myeloid cells. *Anticancer Res* 16:1075-1084, 1996.

72. Oda A, Ozaki K, Druker BJ, Miyakawa Y, Miyazaki H, Handa M, Morita H, Ohashi O, Ikeda Y. $p120^{c\text{-}cbl}$ is present in human blood platelets and is differentially involved in signaling by thrombopoietin and thrombin. *Blood* 88:1330-1338, 1996.

73. Hallek M, Danhauser-Riedl S, Herbst R, Warmuth M, Winkler A, Kolb H-J, Druker B, Griffin JD, Emmerich B, Ullrich A. Interaction of the receptor tyrosine kinase $p145^{c\text{-}kit}$ with the $p210^{bcr/abl}$ kinase in myeloid cells. *Br J Haematol* 94:5-16, 1996.

74. Ottensmeier C, Swanson L, Strobel T, Druker B, Niloff J, Cannistra SA. Absence of constitutive EGF receptor activation in ovarian cancer cell lines. *Br J Cancer* 74:446-452, 1996.

75. Danhauser-Riedl S, Warmuth M, Druker BJ, Emmerich B, Hallek M. Activation of Src kinases p53/p56^{lyn} and p59^{hck} by p210$^{bcr/abl}$ in myeloid cells. *Cancer Res* 56:3589-3596, 1996.

76. Jain SK, Susa M, Keeler ML, Carlesso N, Druker B, Varticovski L. PI 3-kinase activation in BCR/abl-transformed hematopoietic cells does not require interaction of p85 SH2 domain with p210 BCR/abl. *Blood* 88:1542-1550, 1996.

77. Egerton M., Moritz RL, Druker B, Kelso A, Simpson RJ. Identification of the 70kD heat shock cognate protein (Hsc70) and α-actinin-1 as novel phosphotyrosine-containing proteins in T lymphocytes. *Biochem Biophys Res Commun* 224:666-674, 1996.

78. Oda A, Miyakawa Y, Druker BJ, Akaru I, Ozaki K, Ohashi H, Wakui H, Handa M, Watanabe K, Okamoto S, Ikeda Y. Crkl is constitutively tyrosine phosphorylated in platelets from chronic myelogenous leukemia patients and inducibly phosphorylated in normal platelets stimulated by thrombopoietin. *Blood* 88:4304-4313, 1996.

79. Heaney C, Kolibaba K, Bhat A, Oda T, Ohno S, Fanning S, Druker BJ. Direct binding of CRKL to BCR-ABL is not required for BCR-ABL transformation. *Blood* 89:297-306, 1997.

80. Manié SN, Sattler M, Astier A, Phifer JS, Canty T, Morimoto C, Druker BJ, Salgia R, Griffin JD, Freedman AS. Tyrosine phosphorylation of the product of the c-cbl protooncogene is induced after integrin stimulation. *Exp Hematol* 25:45-50, 1997.

81. Manié S, Beck ARP, Astier A, Law SF, Canty T, Hirai H, Druker BJ, Avraham H, Haghayeghi N, Sattler M, Salgia R, Griffin JD, Golemis EA, Freedman AS. Involvement of p130^{Cas} and p105^{HEF1}, a novel Cas-like docking protein, in a cytoskeleton-dependent signaling pathway initiated by ligation of integrin or antigen receptor on human B cells. *J Biol Chem* 272:4230-4236, 1997.

82. Avalos BR, Parker JM, Ware DA, Hunter MG, Sibert KA, Druker BJ. Dissociation of the Jak kinase pathway from G-CSF receptor signaling in neutrophils. *Exp Hematol* 25:160-168, 1997.

83. Miyakawa Y, Oda A, Druker BJ, Ozaki K, Handa M, Ohashi H, Ikeda Y. Thrombopoietin and thrombin induce tyrosine phosphorylation of Vav in human blood platelets. *Blood* 89:2789-2798, 1997.

84. Ganju RK, Hatch WC, Avraham H, Ona MA, Druker B, Avraham S, Groopman JE. RAFTK, a novel member of the focal adhesion kinase family, is phosphorylated and associates with signaling molecules upon activation of mature T lymphocytes. *J Exp Med* 185:1055-1063, 1997.

85. Barber DL, Mason JM, Fukazawa T, Reedquist KA, Druker BJ, Band H, D'Andrea AD. Erythropoietin and interleukin-3 activate tyrosine phosphorylation of CBL and association with CRK adaptor proteins. *Blood* 89:3166-3174, 1997.

86. Manié SA, Astier A, Haghayeghi N, Canty T, Druker BJ, Hirai H, Freedman AS. Regulation of integrin-mediated p130^{Cas} tyrosine phosphorylation in human B cells: a role for p59^{Fyn} and SHP2. *J Biol Chem* 272:15636-15641, 1997.

87. Bhat A, Kolibaba K, Oda T, Ohno-Jones S, Heaney C, Druker BJ. Interactions of CBL with BCR-ABL and CRKL in BCR-ABL-transformed myeloid cells. *J Biol Chem* 272:16170-16175, 1997.

88. Astier A, Manié SN, Avraham H, Hirai H, Law SF, Zhang Y, Golemis EA, Fu Y, Druker BJ, Haghayeghi N, Freedman AS, Avraham S. The related adhesion focal tyrosine kinase differentially phosphorylates p130^{Cas} and the Cas-like protein, p105^{HEF-1}. *J Biol Chem* 272:19719-19724, 1997.

89. Oda T, Kujovich J, Reis M, Newman B, Druker BJ. Identification and characterization of two novel SH2 domain-containing proteins from a yeast two hybrid screen with the ABL tyrosine kinase. *Oncogene* 15:1255-1262, 1997.

90. Hallek M, Neumann C, Schäffer M, Danhauser-Reidl S, von Bubnoff N, de Vos G, Druker BJ, Yasukawa K, Griffin JD, Emmerich B. Signal transduction of interleukin-6 involves tyrosine phosphorylation of multiple cytosolic proteins and activation of Src-family kinases Fyn, Hck, and Lyn in multiple myeloma cell lines. *Exp Hematol* 25:1367-1377, 1997.

91. Astier A, Manie SN, Law S, Canty, T, Haghayghi N, Druker BJ, Salgia R, Golemis EA, Freedman AS. Association of the Cas-like molecule HEF1 with CrkL following integrin and antigen receptor signaling in human B cells. Potential relevance to neoplastic lymphohematopoietic cells. *Leuk Lymphoma* 28:65-72, 1997.

92. Carroll M, Ohno-Jones S, Tamura S, Buchdunger E, Zimmermann J, Lydon NB, Gilliland DG, Druker BJ. CGP 57148, a tyrosine kinase inhibitor, inhibits the growth of cells expressing BCR-ABL, TEL-ABL and TEL-PDGFR fusion proteins. *Blood* 90:4947-4952, 1997.

93. Pestina TI, Stenberg PE, Druker BJ, Steward SA, Hutson NK, Barrie RJ, Jackson CW. Identification of the Src family kinases, Lck and Fgr in platelets: their tyrosine phosphorylation status and subcellular distribution compared with other Src family members. *Arterioscler Thromb Vasc Biol* 17:3278-3285, 1997.

94. Ahmad S, Alsayed YM, Druker BJ, Platanias LC. The type I interferon receptor mediates tyrosine phosphorylation of the CrkL adaptor protein. *J Biol Chem* 272:29991-29994, 1997.

95. Oliveira MLS, Roberts TM, Druker BJ, Armelin MCS. Mapping of polyomavirus middle T domain that is responsible for AP-1 activation. *Oncogene* 16:2975-2982, 1998.

96. Oda A, Sawada K, Druker BJ, Ozaki K, Takano H, Koizumi K, Fukada Y, Handa M, Koike T, Ikeda Y. Erythropoietin induces tyrosine phosphorylation of Jak2, STAT5A and STAT5B in primary cultured human erythroid precursors. *Blood* 92:443-451, 1998.

97. Miyake S, Lupher ML Jr, Druker B, Band H. The tyrosine kinase regulator Cbl enhances the ubiquitination and degradation of the platelet-derived growth factor receptor α. *Proc Natl Acad Sci USA* 95:7927-7932, 1998.

98. Senechal K, Heaney C, Druker B, Sawyers CL. Structural requirements for function of the Crkl adaptor protein in fibroblasts and hematopoietic cells. *Mol Cell Biol* 18:5082-5090, 1998.

99. Oda A, Ochs HD, Druker BJ, Ozaki K, Watanabe C, Handa M, Miyakawa Y, Ikeda Y. Collagen induces tyrosine phosphorylation of Wiskott-Aldrich syndrome protein in human platelets. *Blood* 92:1852-1858, 1998.

100. Bhat A, Johnson K, Oda T, Corbin AS, Druker BJ. Interactions of $p62^{dok}$ with $p210^{bcr-abl}$ and Bcr-Abl associated proteins. *J Biol Chem* 273:32360-32368, 1998.

101. Ozaki K, Oda A, Wakao H, Rhodes J, Druker BJ, Ishida A, Wakui M, Okamoto S, Morita K, Handa M, Komatsu N, Ohashi H, Miyajima A, Ikeda Y. Thrombopoietin induces association of Crkl with STAT5 but not STAT3 in human platelets. *Blood* 92:4652-4662, 1998.

102. Lupher ML Jr, Rao N, Lill NL, Andoniou CE, Miyake S, Clark EA, Druker B, Band H. Cbl-mediated negative regulation of the Syk tyrosine kinase: a critical role for the Cbl phosphotyrosine-binding domain binding to Syk phosphotyrosibe 323. *J Biol Chem* 273:35273-35281, 1998.

103. Fish EN, Uddin S, Korkmaz M, Majchrzak B, Druker BJ, Platanias LC. Activation of a CrkL-Stat5 signaling complex by type I interferons. *J Biol Chem* 274:571-573, 1999.

104. Kolibaba KS, Bhat A, Heaney C, Oda T, Druker BJ. CRKL binding to BCR-ABL and BCR-ABL transformation. *Leuk Lymphoma* 33:119-126. 1999.

105. Tomasson MH, Williams IR, Hasserjian R, Udomsakdi C, McGrath SM, Schwaller J, Druker B, Gilliland DG. TEL/PDGFβR induces hematologic malignancies in mice that respond to a specific tyrosine kinase inhibitor. *Blood* 93:1707-14, 1999.

106. Platanias LC, Uddin S, Bruno E, Korkmaz M, Ahmad S, Alsayed Y, Van Den Berg D, Druker BJ, Wickrema A, Hoffman R. CrkL and CrkII participate in the generation of the growth inhibitory effects of interferons on primary hematopoietic progenitors. *Exp Hematol* 27:1315-21, 1999.

107. Oda A, Miyakawa Y, Druker BJ, Ozaki K, Ohashi H, Kato T, Miyazaki H, Handa M, Ikebuchi K, Ikeda Y. Thrombopoietin-induced signal transduction and potentiation of platelet activation. *Thrombosis and Haemostasis* 82:377-384, 1999.

108. Gaston I, Stenberg PE, Bhat A, Druker BJ. ABL kinase but not PI3-kinase links to the cytoskeletal abnormalities in Bcr-Abl transformed cells. *Exp Hematol* 28:77-86, 2000.

109. Ota S, Hazeki K, Rao N, Lupher ML Jr, Andoniou CE, Druker B, Band H. The RING finger domain of Cbl Is essential for negative regulation of the Syk tyrosine kinase. *J Biol Chem* 275 :414-422, 2000.

110. Oda A, Ikeda Y, Ochs HD, Druker BJ, Ozaki K, Handa M, Ariga T, Sakiyama Y, Witte ON, Wahl MI. Rapid tyrosine phosphorylation and activation of Bruton's tyrosine/Tec kinases in platelets induced by collagen binding or CD32 cross-linking. *Blood* 95:1663-1670, 2000.

111. Rhodes J, York RD, Tara D, Tajinda K, Druker BJ. CrkL functions as a nuclear adaptor and transcriptional activator in Bcr-Abl-expressing cells. *Exp Hematol* 28:305-310, 2000.

112. Alsayed Y, Uddin S, Ahmad S, Majchrzak B, Druker BJ, Bos JL, Fish EN, Platanias LC. IFN-γ activates the C3G/Rap1 signaling pathway. *J Immunol* 164:1800-1806, 2000.

113. Rao N, Lupher ML Jr, Ota S, Reedquist KA, Druker BJ, Band H. The linker phosphorylation site tyr292 mediates the negative regulatory effect of cbl on ZAP-70 in T cells. *J Immunol* 164:4616-4626, 2000.

114. Wilbanks AM, Mahajan S, Frank DA, Druker BJ, Gilliland DG, Carroll M. Tel/PDGFRßR fusion protein activates STAT1 and 5: a common mechanism for transformation by tyrosine kinase fusion proteins. *Exp Hematol* 28:584-593, 2000

115. Alsayed Y, Modi S, Uddin S, Mahmud N, Druker BJ, Fish EN, Hoffman R, Platanias LC. All-trans-retinoic acid induces tyrosine phosphorylation of the CrkL adapter in acute promyelocytic leukemia cells. *Exp Hematol* 28:826-32, 2000.

116. Heinrich MC, Griffith DJ, Druker BJ, Wait CL, Ott KA, Zigler AJ. Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor. *Blood* 96:925-932, 2000.

117. Thiesing JT, Ohno-Jones S, Kolibaba KS, Druker BJ. Efficacy of STI571, an ABL tyrosine kinase inhibitor, in conjunction with other anti-leukemic agents against Bcr-Abl-positive cells. *Blood* 96:3195-3199, 2000.

118. Buchdunger E, Cioffi CL, Law N, Stover D, Ohno-Jones S, Druker BJ, Lydon NB. Abl protein-tyrosine kinase inhibitor STI571 inhibits in vitro signal transduction mediated by c-Kit and platelet-derived growth factor receptors. *J Pharmacol Exp Ther* 295: 39-145, 2000.

119. Grumbach IM, Mayer IA, Uddin S, Lekmine F, Majchrzak B, Yamauchi H., Fujita S, Druker BJ, Fish EN, Platanias LC. Engagement of the CrkL adaptor in interferon alpha signaling in BCR-ABL-expressing cells. *Br J Haematol* 112:327-336, 2001.

120. Guris DL, Fantes J, Tara D, Druker BJ, Imamoto A. Mice lacking the homologue of the human 22q11.2 gene CRKL phenocopy neurocristopathies of DiGeorge syndrome. *Nat Genet* 27:293-298, 2001.

121. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, Lydon NB, Kantarjian H, Capdeville R, Ohno-Jones S, Sawyers CL. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 344:1031-1037, 2001.

122. Druker BJ, Sawyers CL, Kantarjian H, Resta DJ, Fernandes Reese S, Ford JM, Capdeville R, Talpaz M. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N Engl J Med* 344:1038-1042, 2001.

123. Joensuu H, Roberts P, Sarlomo-Rikala M, Andersson LC, Tervahartiala P, Tuveson D, Silberman S, Capdeville R, Dimitrijevic S, Druker BJ, Demetri GD. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med* 344:1052-56, 2001.

124. Goldman JM, Druker BJ. Chronic myeloid leukemia: current treatment options. *Blood* 98:2039-2042, 2001.

125. Hochhaus A, Kreil S, Corbin A, La Rosee P, Lahaye T, Berger U, Cross NC, Linkesch W, Druker BJ, Hehlmann R, Gambacorti- Passerini C, Corneo G, D'Incalci M. Roots of clinical resistance to STI-571 cancer therapy. *Science* 293:2163a, 2001.

126. Rao N, Ghosh AK, Ota S, Zhou P, Reddi AL, Hakezi K, Druker BJ, Wu J, Band H. The non-receptor tyrosine kinase Syk is a target of Cbl-mediated ubiquitylation upon B-cell receptor stimulation. *EMBO J* 20:7085-7095, 2001.

127. Kantarjian H, Sawyers C, Hochhaus A, Guilhot F, Schiffer C, Gambacorti-Passerini C, Diederwieser D, Resta D, Capdeville R, Zoellner U, Talpaz M, Druker B, for the International STI571 CML Study Group. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. *N Engl J Med* 346:645-652, 2002.

128. Lekmine F, Sassano A, Uddin S, Majchrzak B, Miura O, Druker BJ, Fish EN. The CrkL adapter protein is required for type I Interferon-dependent gene transcription and activation of the small G-protein Rap1. *Biochem Biophys Res Commun* 291:744-50, 2002.

129. Talpaz M, Silver RT, Druker BJ, Goldman JM, Gambacorti-Passerini C, Guilhot F, Schiffer CA, Fischer T, Deininger MW, Lennard AL, Hochhaus A, Ottmann OG, Gratwohl A, Baccarani M, Stone R, Tura S, Mahon FX, Fernandes-Reese S, Gathmann I, Capdeville R, Kantarjian HM, Sawyers CL. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. *Blood* 99:1928-1937, 2002.

130. Sawyers CL, Hochhaus A, Feldman E, Goldman JM, Miller CB, Ottmann OG, Schiffer CA, Talpaz M, Guilhot F, Deininger MWN, Fischer T, O'Brien SG, Stone RM, Gambacorti-Passerini CB, Russell NH, Reiffers JJ, Shea TC, Chapuis B, Coutre S, Tura S, Morra E, Larson RA, Saven A, Peschel C, Gratwohl A, Mandelli F, Ben-Am M, Gathmann I, Capdeville R, Paquette RL, Druker BJ. Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. *Blood* 99:3530-3539, 2002.

131. Wertheim JA, Forsythe K, Druker BJ, Hammer D, Boettiger D, Pear WS. BCR-ABL-induced adhesion defects are tyrosine kinase-independent. *Blood* 99:4122-4130, 2002.

132. Dash AB, Williams IR, Kutok JL, Tomasson MH, Anastasiadou E, Lindahl K, Li S, Van Etten RA, Borrow J, Housman D, Druker B, Gilliland DG. A murine model of CML blast crisis induced by cooperation between BCR/ABL and NUP98/HOXA9. *Proc Natl Acad Sci USA* 99:7622-6727, 2002.

133. Braziel RM, Launder TM, Druker BJ, Olson SB, Magenis E, Mauro MJ, Sawyers CL, Paquette RL, O'Dwyer ME. Hematopathologic and cytogenetic findings in imatinib mesylate-treated chronic myelogenous leukemia patients: 14 months' experience. *Blood* 100:435-441, 2002.

134. La Rosee P, O'Dwyer ME, Druker BJ. Insights from pre-clinical studies for new combination treatment regimens with the Bcr-Abl kinase inhibitor imatinib mesylate (Gleevec/Glivec) in chronic myelogenous leukemia: a translational perspective. *Leukemia* 16:1213-1219, 2002.

135. La Rosee P, Johnson K, O'Dwyer ME, Druker BJ. In vitro studies of the combination of imatinib mesylate (Gleevec) and arsenic trioxide (Trisenox) in chronic myelogenous leukemia. *Exp Hematol* 30:729-737, 2002.

136. Moses AV, Jarvis MA, Raggo C, Bell YC, Ruhl R, Luukkonen BG, Griffith DJ, Wait CL, Druker BJ, Heinrich MC, Nelson JA, Fruh K. Kaposi's sarcoma-associated herpesvirus-induced upregulation of the c-kit proto-oncogene, as identified by gene expression profiling, is essential for the transformation of endothelial cells. *J Virol* 76:8383-8399, 2002.

137. Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, Heinrich MC, Tuveson DA, Singer S, Janicek M, Fletcher JA, Silverman SG, Silberman SL, Capdeville R, Kiese B, Peng B, Dimitrijevic S, Druker BJ, Corless C, Fletcher C, Joensuu H. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 347:472:480, 2002.

138. Corbin, AS, Buchdunger E, Pascal F, Druker BJ. Analysis of the structural basis of specificity of inhibition of the Abl kinase by STI571. *J Biol Chem* 277:32214-32219, 2002.

139. O'Dwyer ME, Mauro MJ, Kurilik G, Mori M, Balleisen S, Olson S, Magenis E, Capdeville R, Druker BJ. The impact of clonal evolution on response to imatinib mesylate (STI571) in accelerated phase CML. *Blood* 100:1628-1633, 2002.

140. Ottmann OG, Druker BJ, Sawyers CL, Goldman JM, Reiffers J, Silver RT, Tura S, Fischer T, Deininger MW, Schiffer CA, Baccarani M, Gratwohl A, Hochhaus A, Hoelzer D, Fernandes-Reese S, Gathmann I, Capdeville R, O'Brien SG. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. *Blood* 100:1965-1971, 2002.

141. Hochhaus A, Kreil S, Corbin AS, La Rosee P, Muller MC, Lahaye T, Hanfstein B, Schoch C, Cross NC, Berger U, Gschaidnmeier H, Druker BJ, Hehlmann R. Molecular and chromosomal mechanisms of resistance to imatinib (STI571) therapy. *Leukemia* 16:2190-2196, 2002.

142. La Rosée P, Corbin AS, Stoffregen EP, Deininger MW, Druker BJ. Activity of the Bcr-Abl kinase inhibitor PD180970 against clinically relevant Bcr-Abl isoforms that cause resistance to imatinib mesylate (Gleevec, STI571). *Cancer Res* 62:7149-7153, 2002.

143. Moses AV, Jarvis MA, Raggo C, Bell YC, Ruhl R, Luukkonen BG, Griffith DJ, Wait CL, Druker BJ, Heinrich MC, Nelson JA, Fruh K. A functional genomics approach to Kaposi's sarcoma. *Ann N Y Acad Sci* 975:180-191, 2002.

144. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, Cornelissen JJ, Fischer T, Hochhaus A, Hughes T, Lechner K, Nielsen JL, Rousselot P, Reiffers J, Saglio G, Shepherd J, Simonsson B, Gratwohl A, Goldman JM, Kantarjian H, Taylor K, Verhoef G, Bolton AE, Capdeville R, Druker BJ. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 348:994-1004, 2003.

145. O'Dwyer ME, Gatter KM, Loriaux M, Druker BJ, Olson SB, Magenis RE, Lawce H, Mauro MJ, Maziarz RT, Braziel RM. Demonstration of Philadelphia chromosome negative abnormal clones in patients with chronic myelogenous leukemia during major cytogenetic responses induced by imatinib mesylate. *Leukemia* 17:481-7, 2003.

146. Deininger MW, O'Brien SG, Ford JM, Druker BJ. Practical management of patients with chronic myeloid leukemia receiving imatinib. *J Clin Oncol* 21:1637-47, 2003 [Epub 2003 Mar 13].

147. Kurzrock R, Kantarjian HM, Druker BJ, Talpaz M. Philadelphia chromosome-positive leukemias: from basic mechanisms to molecular therapeutics. *Ann Intern Med* 138:819-830, 2003.

148. Corbin AS, La Rosee P, Stoffregen EP, Druker BJ, Deininger MW. Several Bcr-Abl kinase domain mutants associated with imatinib mesylate resistance remain sensitive to imatinib. *Blood* 101:4611-4614, 2003 [Epub 2003 Feb 06].

149. Hahn EA, Glendenning GA, Sorensen MV, Hudgens SA, Druker BJ, Guilhot F, Larson RA, O'Brien SG, Dobrez DG, Hensley ML, Cella D. Quality of life in patients with newly diagnosed chronic phase chronic myeloid leukemia on imatinib versus interferon alfa plus low-dose cytarabine: results from the IRIS study. *J Clin Oncol* 21:2138-2146, 2003.

150. Frater JL, Tallman MS, Variakojis D, Druker BJ, Resta D, Riley MB, Hrisinko MA, Peterson LC. Chronic myeloid leukemia following therapy with imatinib mesylate (Gleevec). Bone marrow histopathology and correlation with genetic status. *Am J Clin Pathol* 119:833-841, 2003.

151. Miura-Shimura Y, Duan L, Rao NL, Lakku Reddi A, Shimura H, Rottapel R, Druker BJ, Tsygankov A, Band V, Band H. Cbl-mediated ubiquitinylation and negative regulation of Vav. *J Biol Chem* 278:38495-38504, 2003 [Epub 2003 Jul 24].

152. La Rosee P, Johnson K, Corbin AS, Stoffregen EP, Moseson EM, Willis S, Mauro MM, Melo JV, Deininger MW, Druker BJ. In vitro efficacy of combined treatment depends on the underlying mechanism of resistance in imatinib-resistant Bcr-Abl-positive cell lines. *Blood* 103:208-215, 2004 [Epub 2003 Aug 21].

153. Fraunfelder FW, Solomon J, Druker BJ, Esmaeli B, Kuyl J. Ocular side-effects associated with imatinib mesylate (Gleevec). *J Ocul Pharmacol Ther* 19:371-5, 2003.

154. O'Dwyer ME, Mauro MJ, Blasdel C, Farnsworth M, Kurilik G, Hsieh YC, Mori M, Druker BJ. Clonal evolution and lack of cytogenetic response are adverse prognostic factors for hematologic relapse of chronic phase CML patients treated with Imatinib mesylate (STI571). *Blood* 103:451-455, 2004 [Epub 2003 Sep 25].

155. Dinulescu DM, Wood LJ, Shen L, Loriaux M, Corless CL, Gross AW, Ren R, Deininger MW, Druker BJ. c-CBL is not required for leukemia induction by Bcr-Abl in mice. *Oncogene* 22:8852-60, 2003.

156. Heinrich MC, Corless CL, Demetri GD, Blanke CD, von Mehren M, Joensuu H, McGreevey LS, Chen CJ, Van den Abbeele AD, Druker BJ, Kiese B, Eisenberg B, Roberts PJ, Singer S, Fletcher CD, Silberman S, Dimitrijevic S, Fletcher JA. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *J Clin Oncol* 21:4342-4349, 2003.

157. La Rosee P, Shen L, Stoffregen EP, Deininger M, Druker BJ. No correlation between the proliferative status of Bcr-Abl positive cell lines and the proapoptotic activity of imatinib mesylate (Gleevec/Glivec). *Hematol J* 4:413-419, 2003.

158. Lim YP, Diong LS, Qi R, Druker BJ, Epstein RJ. Phosphoproteomic fingerprinting of epidermal growth factor signaling and anticancer drug action in human tumor cells. *Mol Cancer Ther* 2:1369-1377, 2003.

159. Gaston I, Johnson KJ, Oda T, Bhat A, Reis M, Langdon W, Shen L, Deininger MW, Druker BJ. Coexistence of phosphotyrosine-dependent and -independent interactions between Cbl and Bcr-Abl. *Exp Hematol* 32:113-121, 2004.

160. Al-Ali HK, Heinrich MC, Lange T, Krahl R, Mueller M, Muller C, Niederwieser D, Druker BJ, Deininger MW. High incidence of BCR-ABL kinase domain mutations and absence of mutations of the PDGFR and KIT activation loops in CML patients with secondary resistance to imatinib. *Hematol J* 5:55-60, 2004.

161. Peng B, Hayes M, Resta D, Racine-Poon A, Druker BJ, Talpaz M, Sawyers CL, Rosamilia M, Ford J, Lloyd P, Capdeville R. Pharmacokinetics and pharmacodynamics of imatinib in a phase I trial with chronic myeloid leukemia patients. *J Clin Oncol* 22:935-942, 2004.

162. Deininger MW, McGreevey L, Willis S, Bainbridge TM, Druker BJ, Heinrich MC. Detection of ABL kinase domain mutations with denaturing high-performance liquid chromatography. *Leukemia* 18:864-871, 2004 [Epub 2004 Feb 19].

163. Mauro MJ, Druker BJ, Maziarz RT. Divergent clinical outcome in two CML patients who discontinued imatinib therapy after achieving a molecular remission. *Leuk Res* 28 Suppl 1:71-73, 2004.

164. Leis JF, Stepan DE, Curtin PT, Ford JM, Peng B, Schubach S, Druker BJ, Maziarz RT. Central nervous system failure in patients with chronic myelogenous leukemia lymphoid blast crisis and Philadelphia chromosome positive acute lymphoblastic leukemia treated with imatinib (STI-571). *Leuk Lymphoma* 45:695-698, 2004.

165. Lim YP, Wong CY, Ooi LL, Druker BJ, Epstein RJ. Selective tyrosine hyperphosphorylation of cytoskeletal and stress proteins in primary human breast cancers: implications for adjuvant use of kinase-inhibitory drugs. *Clin Cancer Res* 10:3980-3987, 2004.

166. Griswold IJ, Shen LJ, LaRosee P, Demehri S, Heinrich MC, Braziel RM, McGreevey L, Haley AD, Giese N, Druker BJ, Deininger MW. Effects of MLN518, a dual FLT3 and KIT inhibitor, on normal and malignant hematopoiesis. *Blood* 104:2912-2918, 2004 [Epub 2004 Jul 8].

167. O'Hare T, Pollock R, Stoffregen EP, Keats JA, Abdullah OM, Moseson EM, Rivera VM, Tang H, Metcalf CA 3rd, Bohacek RS, Wang Y, Sundaramoorthi R, Shakespeare WC, Dalgarno D, Clackson T, Sawyer TK, Deininger MW, Druker BJ. Inhibition of wild-type and mutant Bcr-Abl by AP23464, a potent ATP-based oncogenic protein kinase inhibitor: implications for CML. *Blood* 104:2532-2539, 2004 [Epub 2004 Jul 15].

168. Corbin AS, Griswold IJ, La Rosee P, Yee KW, Heinrich MC, Reimer CL, Druker BJ, Deininger MW. Sensitivity of oncogenic KIT mutants to the kinase inhibitors MLN518 and PD180970. *Blood* 104:3754-3757, 2004 [Epub 2004 Aug 10].

169. Leis JF, Primack SL, Schubach SE, Curtin PT, Druker BJ, Maziarz RT. Management of life-threatening pulmonary leukostasis with single agent imatinib mesylate during CML myeloid blast crisis. *Haematologica* 89:ECR30, 2004.

170. Grossmann AH, Kolibaba KS, Willis SG, Corbin AS, Langdon WS, Deininger MW, Druker BJ. Catalytic domains of tyrosine kinases determine the phosphorylation sites within c-Cbl. *FEBS Lett* 577:555-562, 2004.

171. Walters DK, Stoffregen EP, Heinrich MC, Deininger MW, Druker BJ. RNAi-induced down-regulation of FLT3 expression in AML cell lines increases sensitivity to MLN518. *Blood* 105:2952-2954, 2005 [Epub 2004 Dec 7].

172. Deininger M, Buchdunger E, Druker BJ. The development of imatinib as a therapeutic agent for chronic myeloid leukemia. *Blood* 105:2640-2653, 2005 [Epub 2004 Dec 23].

173. Tseng PH, Lin HP, Zhu J, Chen KF, Hade EM, Young DC, Byrd JC, Grever M, Johnson K, Druker BJ, Chen CS. Synergistic interactions between imatinib and the novel phosphoinositide-dependent kinase-1 inhibitor OSU-03012 in overcoming imatinib mesylate resistance. *Blood* 105:4021-7, 2005 [Epub 2005 Jan 21].

174. Demehri S, Paschka P, Schultheis B, Lange T, Koizumi T, Sugimoto T, Branford S, Lim LC, Kegel T, Martinelli G, Hochhaus A, Druker BJ, Deininger MW. e8a2 BCR-ABL: more frequent than other atypical BCR-ABL variants? *Leukemia* 19:681-684, 2005 [Epub 2005 Feb 10].

175. Corbin AS, Demehri S, Griswold IJ, Wang Y, Metcalf Iii CA, Sundaramoorthi R, Shakespeare WC, Snodgrass J, Wardwell S, Dalgarno D, Iuliucci J, Sawyer T, Heinrich MC, Druker BJ, Deininger MW. In vitro and in vivo activity of ATP-based kinase inhibitors AP23464 and AP23848 against activation-loop mutants of Kit. *Blood* 106:227-234, 2005 [Epub 2005 Mar 3].

176. Mayerhofer M, Aichberger KJ, Florian S, Krauth MT, Hauswirth AW, Derdak S, Sperr WR, Esterbauer H, Wagner O, Marosi C, Pickl WF, Deininger M, Weisberg E, Druker BJ, Griffin JD, Sillaber C, Valent P. Identification of mTOR as a novel bifunctional target in chronic myeloid leukemia: dissection of growth-inhibitory and VEGF-suppressive effects of rapamycin in leukemic cells. *FASEB J* 19:960-962, 2005 [Epub 2005 Mar 22].

177. Crossman LC, Mori M, Hsieh YC, Lange T, Paschka P, Harrington CA, Krohn K, Niederwieser DW, Hehlmann R, Hochhaus A, Druker BJ, Deininger MW. In chronic myeloid leukemia white cells from cytogenetic responders and non-responders to imatinib have very similar gene expression signatures. *Haematologica* 90:459-464, 2005.

178. Willis SG, Lange T, Demehri S, Otto S, Crossman L, Niederwieser D, Stoffregen EP, McWeeney S, Kovacs I, Park B, Druker BJ, Deininger MW. High-sensitivity detection of BCR-ABL kinase domain mutations in imatinib-naive patients: correlation with clonal cytogenetic evolution but not response to therapy. *Blood* 106:2128-2137, 2005 [Epub 2005 May 24].

179. O'Hare T, Walters DK, Stoffregen EP, Jia T, Manley PW, Mestan J, Cowan-Jacob SW, Lee FY, Heinrich MC, Deininger MWN, Druker BJ. In vitro activity of Bcr-Abl inhibitors AMN107 and BMS-354825 against clinically relevant imatinib-resistant Abl kinase domain mutants. *Cancer Res* 65:4500-4505, 2005.

180. Levine RL, Loriaux M, Huntly BJ, Loh ML, Beran M, Stoffregen E, Berger R, Clark JJ, Willis SG, Nguyen KT, Flores NJ, Estey E, Gattermann N, Armstrong S, Look AT, Griffin JD, Bernard OA, Heinrich MC, Gilliland DG, Druker B, Deininger MW. The JAK2V617F activating mutation occurs in chronic myelomonocytic leukemia and acute myeloid leukemia, but not in acute lymphoblastic leukemia or chronic lymphocytic leukemia. *Blood* 106:3377-3379, 2005 [Epub 2005 Aug 4].

181. Crossman LC, O'Hare T, Lange T, Willis SG, Stoffregen EP, Corbin AS, O'Brien SG, Heinrich MC, Druker BJ, Middleton PG, Deininger MW. A single nucleotide polymorphism in the coding region of ABL and its effects on sensitivity to imatinib. *Leukemia* 19:1859-1862, 2005 [Epub 2005 Sep 8].

182. Chuah C, Barnes DJ, Kwok M, Corbin A, Deininger MW, Druker BJ, Melo JV. Zoledronate inhibits proliferation and induces apoptosis of imatinib-resistant chronic myeloid leukaemia cells. *Leukemia* 19:1896-1904, 2005 [Epub 2005 Sep 15].

183. O'Hare T, Walters DK, Stoffregen EP, Sherbenou DW, Heinrich MC, Deininger MW, Druker BJ. Combined abl inhibitor therapy for minimizing drug resistance in chronic myeloid leukemia: src/abl inhibitors are compatible with imatinib. *Clin Cancer Res* 11:6987-6993, 2005.

184. Aichberger KJ, Mayerhofer M, Krauth MT, Vales A, Kondo R, Derdak S, Pickl WF, Selzer E, Deininger M, Druker BJ, Sillaber C, Esterbauer H, Valent P. Low-level expression of proapoptotic Bcl-2-interacting mediator in leukemic cells in patients with chronic myeloid leukemia: role of BCR/ABL, characterization of underlying signaling pathways, and reexpression by novel pharmacologic compounds. *Cancer Res* 65:9436-9444, 2005.

185. Schittenhelm MM, Shiraga S, Schroeder A, Corbin AS, Griffith D, Lee FY, Bokemeyer C, Deininger MW, Druker BJ, Heinrich MC. Dasatinib (BMS-354825), a dual SRC/ABL kinase inhibitor, inhibits the kinase activity of wild-type, juxtamembrane, and activation loop mutant KIT isoforms associated with human malignancies. *Cancer Res* 66:473-481, 2006.

186. Walters DK, Goss VL, Stoffregen EP, Gu TL, Lee K, Nardone J, McGreevey L, Heinrich MC, Deininger MW, Polakiewicz R, Druker BJ. Phosphoproteomic analysis of AML cell lines identifies leukemic oncogenes. *Leuk Res* 30:1097-1104, 2006 [Epub 2006 Feb 7].

187. Press RD, Love Z, Tronnes AA, Yang R, Tran T, Mongoue-Tchokote S, Mori M, Mauro MJ, Deininger MW, Druker BJ. BCR-ABL mRNA levels at and after the time of a complete cytogenetic response (CCR) predict the duration of CCR in imatinib mesylate-treated patients with CML. *Blood* 107:4250-4256, 2006 [Epub 2006 Feb 7].

188. Radich JP, Dai H, Mao M, Oehler V, Schelter J, Druker B, Sawyers C, Shah N, Stock W, Willman CL, Friend S, Linsley PS. Gene expression changes associated with progression and response in chronic myeloid leukemia. *Proc Natl Acad Sci U S A* 103:2794-2799, 2006 [Epub 2006 Feb 13].

189. Hughes T, Deininger M, Hochhaus A, Branford S, Radich J, Kaeda J, Baccarani M, Cortes J, Cross NC, Druker BJ, Gabert J, Grimwade D, Hehlmann R, Kamel-Reid S, Lipton JH, Longtine J, Martinelli G, Saglio G, Soverini S, Stock W, Goldman JM. Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. *Blood* 108:28-37, 2006 [Epub 2006 Mar 7].

190. Demehri S, Corbin A, Loriaux M, Druker BJ, Deininger MW. Establishment of a murine model of aggressive systemic mastocytosis/mast cell leukemia. *Exp Hematol* 34:284-288, 2006.

191. Deininger M, Schleuning M, Greinix H, Sayer HG, Fischer T, Martinez J, Maziarz R, Olavarria E, Verdonck L, Schaefer K, Boqui C, Faber E, Nagler A, Pogliani E, Russell N, Volin L, Schanz U, Doelken G, Kiehl M, Fauser A, Druker B, Sureda A, Iacobelli S, Brand R, Krahl R, Lange T, Hochhaus A, Gratwohl A, Kolb H, Niederwieser D. The effect of prior exposure to imatinib on transplant-related mortality. *Haematologica* 91:452-459, 2006.

192. Nguyen TK, Rahmani M, Gao N, Kramer L, Corbin AS, Druker BJ, Dent P, Grant S. Synergistic Interactions between DMAG and Mitogen-Activated Protein Kinase Kinase 1/2 Inhibitors in Bcr/abl+ Leukemia Cells Sensitive and Resistant to Imatinib Mesylate. *Clin Cancer Res* 12:2239-2247, 2006.

193. Roy L, Guilhot J, Krahnke T, Guerci-Bresler A, Druker BJ, Larson RA, O'Brien S, So C, Massimini G, Guilhot F. Survival advantage from imatinib compared with the combination interferon-alpha plus cytarabine in chronic-phase chronic myelogenous leukemia: historical comparison between two phase 3 trials. *Blood* 108:1478-1484, 2006 [Epub 2006 Apr 20].

194. Bradeen HA, Eide CA, O'hare T, Johnson KJ, Willis SG, Lee FY, Druker BJ, Deininger MW. Comparison of imatinib mesylate, dasatinib (BMS-354825), and nilotinib (AMN107) in an N-ethyl-N-nitrosourea (ENU)-based mutagenesis screen: high efficacy of drug combinations. *Blood* 108:2332-2338, 2006 [Epub 2006 Jun 13].

195. Walters DK, Mercher T, Gu TL, O'hare T, Tyner JW, Loriaux M, Goss VL, Lee KA, Eide CA, Wong MJ, Stoffregen EP, McGreevey L, Nardone J, Moore SA, Crispino J, Boggon TJ, Heinrich MC, Deininger MW, Polakiewicz RD, Gilliland DG, Druker BJ. Activating alleles of JAK3 in acute megakaryoblastic leukemia. *Cancer Cell* 10:65-75, 2006.

196. Griswold IJ, Macpartlin M, Bumm T, Goss VL, O'hare T, Lee KA, Corbin AS, Stoffregen EP, Smith C, Johnson K, Moseson EM, Wood LJ, Polakiewicz RD, Druker BJ, Deininger MW. Kinase domain mutants of bcr-abl exhibit altered transformation potency, kinase activity, and substrate utilization, irrespective of sensitivity to imatinib. *Mol Cell Biol* 26:6082-6093, 2006.

197. Deangelo DJ, Stone RM, Heaney ML, Nimer SD, Paquette RL, Klisovic RB, Caligiuri MA, Cooper MR, Lecerf JM, Karol MD, Sheng S, Holford N, Curtin PT, Druker BJ, Heinrich MC. Phase 1 clinical results with tandutinib (MLN518), a novel FLT3 antagonist, in patients with acute myelogenous leukemia or high-risk myelodysplastic syndrome: safety, pharmacokinetics, and pharmacodynamics. *Blood* 108:3674-3681 [Epub 2006 Aug 10].

198. Gu TL, Goss VL, Reeves C, Popova L, Nardone J, Macneill J, Walters DK, Wang Y, Rush J, Comb MJ, Druker BJ, Polakiewicz RD. Phosphotyrosine profiling identifies the KG-1 cell line as a model for the study of FGFR1 fusions in acute myeloid leukemia. *Blood* 108:4202-4204,2006 [Epub 2006 Aug 31].

199. Kuroda J, Puthalakath H, Cragg MS, Kelly PN, Bouillet P, Huang DC, Kimura S, Ottmann OG, Druker BJ, Villunger A, Roberts AW, Strasser A. Bim and Bad mediate imatinib-induced killing of Bcr/Abl+ leukemic cells, and resistance due to their loss is overcome by a BH3 mimetic. *Proc Natl Acad Sci U S A* 103:14907-14912, 2006 [Epub 2006 Sep 22].

200. Chen J, Yu WM, Daino H, Broxmeyer HE, Druker BJ, Qu CK. SHP-2 phosphatase is required for hematopoietic cell transformation by Bcr-Abl. *Blood* 2006 Sep 26 [Epub ahead of print].

201. Wood LJ, Nail LM, Perrin NA, Elsea CR, Fischer A, Druker BJ. The cancer chemotherapy drug etoposide (VP-16) induces proinflammatory cytokine production and sickness behavior-like symptoms in a mouse model of cancer chemotherapy-related symptoms. *Biol Res Nurs* 8:157-169, 2006.

202. La Rosee P, Jia T, Demehri S, Hartel N, de Vries P, Bonham L, Hollenback D, Singer JW, Melo JV, Druker BJ, Deininger MW. Antileukemic Activity of Lysophosphatidic Acid Acyltransferase-{beta} Inhibitor CT32228 in Chronic Myelogenous Leukemia Sensitive and Resistant to Imatinib. *Clin Cancer Res* 12:6540-6546, 2006.

203. Hochhaus A, Kantarjian HM, Baccarani M, Lipton JH, Apperley JF, Druker BJ, Facon T, Goldberg SL, Cervantes F, Niederwieser D, Silver RT, Stone RM, Hughes TP, Muller MC, Ezzeddine R, Countouriotis AM, Shah NP. Dasatinib induces notable hematologic and cytogenetic responses in chronic phase chronic myeloid leukemia after failure of imatinib therapy. *Blood* 2006 Nov 30 [Epub ahead of print].

204. Bumm TG, Elsea C, Corbin AS, Loriaux M, Sherbenou D, Wood L, Deininger J, Silver RT, Druker BJ, Deininger MW. Characterization of Murine JAK2V617F-Positive Myeloproliferative Disease. *Cancer Res* 66:11156-11165.

205. Druker BJ, Guilhot F, O'Brien SG, Gathmann I, Kantarjian H, Gattermann N, Deininger MWN, Silver RT, Goldman JM, Stone RM, Cervantes F, Hochhaus A, Powell BL, Gabrilove JL, Rousselot P, Reiffers J, Cornelissen JJ, Hughes T, Agis H, Fischer T, Verhoef G, Shepherd J, Saglio G, Gratwohl A, Nielsen JL, Radich JP, Simonsson B, Taylor K, Baccarani M, So C, Letvak L, Larson R, for the IRIS Investigators. Five-year follow- up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med* 355:2408-2417, 2006.

Books and Monographs

1. Roberts TM, Kaplan D, Morgan W, Keller T, Mamon H, Piwnica-Worms H, Druker B, Cohen B, Schaffhausen B, Whitman M, Cantley L, Rapp U, Morrison D. Tyrosine phosphorylation in signal transduction. *Cold Spring Harbor Symp Quant Biol* 53:161-171, 1988.
2. Pallas D, Druker B, Mamon H, Li P, Shahrik L, Martin BL, Brautigan DL, Jaspers S, Miller TB, Serunian L, Cantley L, Schaffhausen B, Roberts T. Interactions of polyoma virus T antigens with host cell proteins. In: Papas T, ed. *Advances in Applied Biotechnology Series: Gene Regulation and AIDS.* Houston TX: Gulf Publishing Company, 7:95-106, 1990.
3. Druker BJ, Ohno S, Buchdunger E, Tamura S, Segal GM, Zimmermann J, Lydon NB. Selective killing of BCR-ABL positive cells with a specific inhibitor of the ABL tyrosine kinase. In: Mihich E and Hausman D, eds. *Cancer Genes: Functional Aspects.* New York NY: Plenum Press, 1996: 255-267.
4. Druker BJ. ABL protein tyrosine kinase inhibitors: potential clinical role in CML. In: M Talpaz and H Kantarjian, eds. *Medical Management of Chronic Myelogenous Leukemia.* New York NY: Marcel Dekker, Inc., 1999: 395-411.
5. Rhodes J and Druker BJ. Jak-STAT Signal Transduction. In: Zon LI, ed. *Hematopoiesis: a developmental approach.* New York: Oxford University Press, 2001: 269-287.
6. O'Dwyer ME, Mauro MJ, Druker BJ. STI571 as a therapeutic agent. In: Carella AM, Daley GQ, Eaves CJ, Goldman JM, Hehlmann R, eds. *Chronic Myeloid Leukemia - Biology and Treatment.* London: Martin Dunitz, 2001: 501-505.
7. Druker B. Tyrosine kinase inhibitors in the treatment of chronic myelogenous leukemia. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Progress in Oncology 2001.* Sudbury: Jones and Bartlett Publishers, 2001: 191-203.
8. O'Dwyer ME, Druker BJ. Targeting oncogenes in hematopoietic malignancies. In: Rak J, ed. *Oncogene-Directed Therapies*. Totowa: Humana Press, 2002: 297-311.
9. O'Dwyer ME, Druker BJ. Signal Transduction Inhibitors. In: Kalaycio M, ed. *Biologic Therapy of Leukemia.* Totowa: Humana Press Inc., 2003: 127-144.
10. Heinrich MC, Blanke CD, Corless CL, Druker BJ. Small-Molecular Inhibitors of Protein Kinases in the Treatment of Human Cancer. In: Kufe DW, Pollock RE, Weichselbaum RR, Bast RC, Gansler TS, Holland JF, Frei E III, eds. *Cancer Medicine 6*. Hamilton: BC Decker Inc., 2003: 811-821.
11. Druker BJ. The present and future of molecularly targeted therapy. In: Abeloff MD, Armitage JO, Niederhuber JE, Kastan MB, McKenna WG, eds. *Clinical Oncology, 3rd Edition.* Philadelphia: Elsevier, Inc., 2004: 623-637.
12. Druker BJ, Goldman JM. Chronic myeloid leukemia. In: Abeloff MD, Armitage JO, Niederhuber JE, Kastan MB, McKenna WG, eds. *Clinical Oncology, 3rd Edition.* Philadelphia: Elsevier, Inc., 2004: 2899-2919.
13. Druker BJ. Imatinib as a paradigm of targeted therapies. In: Vande Woude GF, Klein G, eds. *Advances in Cancer Research*. San Diego: Elsevier Academic Press, 2004, vol 91:1-30.
14. Druker BJ. Clinical Aspects of Imatinib Therapy. In: Pinna LA, Cohen PTW, eds. *Handbook of Experimental Pharmacology, Vol 167.* Berlin Heidelberg: Springer-Verlag, 2005:391-410.

15. Druker BJ, Lee SJ. Chronic Leukemias. In: DeVita VT, Rosenberg SA, Hellman S, eds. *Cancer: Principles and Practice of Oncology, 7th Ed.* Philadelphia: Lippincott Williams & Wilkins, 2005, 2121-2133.
16. Druker BJ. Chronic myeloid leukemia. In: Provan D, Gribben JG, eds. *Molecular Hematology, 2nd Ed.* Oxford: Blackwell Publishing, 2005, 72-81.
17. Chabner BA, Amrein PC, DrukerBJ, Michaelson MD, Mitsiades CS, Goss PE, Ryan DP, Ramachandra S, Richardson PG, Supko JG, Wilson WH. Antineoplastic Agents. In: Brunton LL, ed. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 11/E.* New York: McGraw-Hill, 2006: 1315-1403.
18. Heinrich MC, Blanke CD, Corless CL, Druker BJ. Small-Molecular Inhibitors of Protein Kinases in the Treatment of Human Cancer. In: Kufe DW, Bast RC, Hait WN, Hong WK, Pollock RE, Weichselbaum RR, Holland JF, Frei E III, eds. *Cancer Medicine 7*. Hamilton: BC Decker Inc., 2006: 722-732.
19. Druker BJ. Chronis Myelogenous Leukemia. In: Runge MS, Patterson C, eds. *Principles of Molecular Medicine*. Totowa: Humana Press, 2006: 789-793.
20. Deininger MMW, Druker BJ. Chronic Myelogenous Leukemia. In: Boyiadzis MM, Lebowitz PF, Frame JN, Fojo T, eds. *Hematology-Oncology Therapy*. New York: McGraw-Hill, 2006: 248-256.

Invited Articles and Reviews

1. Kolibaba KS and Druker BJ. Acute Leukemia in a Pregnant Woman. *Cancer Practice 4*:299-300, 1996.
2. Kolibaba KS and Druker BJ. Tyrosine Kinases: Their Role in Producing Endocrine and Other Cancers. *Growth, Genetics & Hormones* 13:38-43, 1997.
3. Kolibaba KS and Druker BJ. Protein tyrosine kinases and cancer. *Biochim Biophys Acta* 1333:F217-248, 1997.
4. Sawyers CL and Druker B. Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia. Cancer *J Sci Am* 5: 63-69, 1999.
5. Kolibaba KS and Druker BJ. Current Status of Treatment of CML. *Medscape Oncology*, 3, 2000.
6. Druker BJ and Lydon NB. Lessons learned from the development of an Abl tyrosine kinase inhibitor for chronic myelogenous leukemia. *J Clin Invest* 105: 3-7, 2000.
7. O'Dwyer ME, Druker BJ. Status of *bcr-abl* tyrosine kinase inhibitors in chronic myelogenous leukemia. *Curr Opin Oncol* 12:594-597, 2000.
8. O'Dwyer ME, Druker BJ. STI571: an inhibitor of the BCR-ABL tyrosine kinase for the treatment of chronic myelogenous leukaemia. *Lancet* 1:207-211, 2000.
9. Mauro MJ, Druker BJ. Chronic myelogenous leukemia. *Curr Opin Oncol* 13:3-7, 2001.
10. Mauro MJ, Druker BJ. STI571: Targeting BCR-ABL as Therapy for CML. *Oncologist* 6:233-238, 2001.
11. O'Dwyer ME, Druker BJ. The role of the tyrosine kinase inhibitor STI571 in the treatment of cancer. *Current Cancer Drug Targets* 1:49-57, 2001.
12. Mauro MJ, Druker BJ. STI571: a gene product-targeted therapy for leukemia. *Curr Oncol Rep* 3:223-227, 2001.
13. O'Dwyer ME, Druker BJ. Chronic myelogenous leukaemia—new therapeutic principles. *J Intern Med* 250:3-9, 2001.
14. Druker BJ. Current treatment approaches for chronic myelogenous leukemia. *Cancer J* 7:S14-18, 2001.
15. Druker B. Signal transduction inhibition: results from phase I clinical trials in chronic myeloid leukemia. *Semin Hematol* 38:9-14, 2001.

16. Buchdunger E, Matter A, Druker BJ. Bcr-Abl inhibition as a modality of CML therapeutics. *Biochim Biophys Acta* 1551:M11-18, 2001.
17. Mauro MJ, O'Dwyer ME, Druker BJ. ST1571, a tyrosine kinase inhibitor for the treatment of chronic myelogenous leukemia: validating the promise of molecularly targeted therapy. *Cancer Chemother Pharmacol* 48:S77-78, 2001.
18. Mauro MJ, O'Dwyer ME, Druker BJ. Development of STI571 and Its Use in Chronic Myelogenous Leukemia and Other Malignancies. *Oncology Spectrums* 2:536-541, 2001.
19. Druker BJ. New Approaches to Chronic Myelogenous Leukemia. *Clin Oncol* 4:1-8, 2001.
20. Druker BJ. Imatinib: a viewpoint by Brian J. Druker. *Drugs* 61:1775-1776, 2001.
21. Druker BJ. STI571: a paradigm for clinical trials of molecularly targeted agents. *Biomed Pharmacother* 55:529-30, 2001.
22. Druker BJ. Chronic myeloid leukemia: Sceptical scientists. *Lancet* 358:11, 2001.
23. Druker BJ. Investigator Profile. *J Hematother Stem Cell Res* 10:721-724, 2001.
24. Mauro MJ, O'Dwyer M, Heinrich MC, Druker BJ. STI571: a paradigm of new agents for cancer therapeutics. *J Clin Oncol* 20:325-334, 2002.
25. O'Dwyer ME, Mauro MJ, Druker BJ. Recent Advances in the Treatment of Chronic Myelogenous Leukemia. *Annu Rev Med* 53:369-81, 2002.
26. Druker BJ. Perspectives on the development of a molecularly targeted agent. *Cancer Cell* 1:31-36, 2002.
27. Druker BJ. STI571 (Gleevec™) as a paradigm for cancer therapy. *Trends Mol Med* 8:S14-18, 2002.
28. Heinrich MC, Blanke CD, Druker BJ, Corless CL. Inhibition of KIT tyrosine kinase activity: a novel molecular approach to the treatment of KIT-positive malignancies. *J Clin Oncol* 20:1692-1703, 2002.
29. O'Dwyer ME, La Rosée P, Nimmanapalli R, Bhalla KN, Druker BJ. Recent advances in Philadelphia chromosome-positive malignancies: The potential role of arsenic trioxide. *Semin Hematol* 39:18-21, 2002.
30. Druker BJ. Update on imatinib therapy for chronic myeloid leukemia. *Principles & Practice of Oncology Updates* 16:1-10, 2002.
31. Druker BJ. Imatinib and chronic myeloid leukemia: validating the promise of molecularly targeted therapy. *Eur J Cancer* 38:S70-S76, 2002.
32. Druker BJ. Taking Aim at Ewing's Sarcoma: Is KIT a Target and Will Imatinib Work? *J Natl Cancer Inst* 94:1660-1661, 2002.
33. Deininger MWN and Druker BJ. Molecular targeted therapy: the experience with STI571 (imatinib, Gleevec/Glivec). *Signal* 3:4-9, 2002.
34. Druker BJ. Inhibition of the Bcr-Abl tyrosine kinase as a therapeutic strategy for CML. *Oncogene* 21:8541-8546, 2002.
35. Druker BJ. Imatinib alone and in combination for chronic myeloid leukemia. *Semin Hematol* 40:50-58, 2003.
36. Druker BJ. Overcoming resistance to imatinib by combining targeted agents. *Mol Cancer Ther* 2:225-6, 2003.
37. Druker BJ. Chronic myeloid leukemia in the imatinib era. *Semin Hematol* 40 (suppl 3):1-3, 2003.
38. Druker BJ. Comments on the Hammersmith policy. *Semin Hematol* 40 (suppl 3):107-108, 2003.
39. Druker BJ. Imatinib mesylate in the treatment of chronic myeloid leukaemia. *Expert Opin Pharmacother* 4:963-971, 2003.

40. O'Dwyer ME, Mauro MJ, Druker BJ. STI571 as a targeted therapy for CML. *Cancer Invest* 21:429-438, 2003.
41. Deininger MW, Druker BJ. Specific targeted therapy of chronic myelogenous leukemia with imatinib. *Pharmacol Rev* 55:401-423, 2003 [Epub 2003 Jul 17].
42. Druker BJ. David A. Karnofsky award lecture: Imatinib as a paradigm of targeted therapies. *J Clin Oncol* 21(23 Suppl):239s-245s, 2003.
43. Druker BJ. Can we cure CML? *Blood* 103:2865-2866, 2004.
44. Lydon NB, Druker BJ. Lessons learned from the development of imatinib. *Leuk Res* 28 Suppl 1:29-38, 2004.
45. Druker BJ. Imatinib: Paradigm or Anomaly? *Cell Cycle* 3:833-835, 2004 [Epub 2004 Jul 8].
46. Druker BJ. Molecularly targeted therapy: have the floodgates opened? *Oncologist* 9:357-360, 2004.
47. Deininger MW, Druker BJ. SRCircumventing imatinib resistance. *Cancer Cell* 6:108-110, 2004.
48. O'Hare T, Walters DK, Deininger MW, Druker BJ. AMN107: Tightening the grip of imatinib. *Cancer Cell* 7:117-119, 2005.
49. Aebersold R, Anderson L, Caprioli R, Druker B, Hartwell L, Smith R. Perspective: a program to improve protein biomarker discovery for cancer. *J Proteome Res* 4:1104-1109, 2005.
50. Druker BJ. Tyrosine kinase inhibitors. *Principles & Practice of Oncology Updates* 19:1-11, 2005.
51. O'Hare T, Corbin AS, Druker BJ. Targeted CML therapy: controlling drug resistance, seeking cure. *Curr Opin Genet Dev* 16:92-99, 2006 [Epub 2005 Dec 7].
52. Druker BJ. Circumventing resistance to kinase-inhibitor therapy. *N Engl J Med* 354:2594-2596, 2006.

Published Letters

1. Goldman JM, Druker BJ. Age and chronic myelogenous leukemia treatment algorithm. *Blood* 99:3071, 2002.
2. Corbin A, La Rosée P Stoffregen E, Druker B, Deininger M. Imatinib resistance may be more complex than impaired inhibitor binding. *Blood* 102:1934-1935, 2003.
3. Crossman LC, Druker BJ, Deininger MW, Pirmohamed M, Wang L, Clark RE. hOCT 1 and resistance to imatinib. *Blood* 106:1133-1134, 2005.
4. O'Hare T, Druker BJ. BIRB-796 is not an effective ABL(T315I) inhibitor. *Nat Biotechnol* 23:1209-1210, 2005.

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EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
University of Oregon, Eugene, Oregon	BA	1998	Biochemistry

Experience

1996-1997 Biology Laboratory Teaching Assistant
1997-1998 Department of Biology, University of Oregon, Eugene

1998-2001 Research Assistant, Brian J. Druker, MD
Division of Hematology & Medical Oncology, Oregon Health & Science University (OHSU), Portland

2001-2003 Senior Research Assistant, Brian J. Druker, MD
Division of Hematology & Medical Oncology, OHSU, Portland

2003-present Research Technician III, Brian J. Druker, MD
Howard Hughes Medical Institute, Oregon Health & Science University, Portland

Publications

1. Corbin, AS, Buchdunger E, Pascal F, Druker BJ. Analysis of the structural basis of specificity of inhibition of the Abl kinase by STI571. *J Biol Chem* 277:32214-32219, 2002.
2. Hochhaus A, Kreil S, Corbin AS, La Rosee P, Muller MC, Lahaye T, Hanfstein B, Schoch C, Cross NC, Berger U, Gschaidnmeier H, Druker BJ, Hehlmann R. Molecular and chromosomal mechanisms of resistance to imatinib (STI571) therapy. *Leukemia* 16:2190-2196, 2002.
3. La Rosée P, Corbin AS, Stoffregen EP, Deininger MW, Druker BJ. Activity of the Bcr-Abl kinase inhibitor PD180970 against clinically relevant Bcr-Abl isoforms that cause resistance to imatinib mesylate (Gleevec, STI571). *Cancer Res* 62:7149-7153, 2002.
4. Corbin AS, La Rosee P, Stoffregen EP, Druker BJ, Deininger MW. Several Bcr-Abl kinase domain mutants associated with imatinib mesylate resistance remain sensitive to imatinib. *Blood* 101:4611-4614, 2003 [Epub 2003 Feb 06].
5. La Rosee P, Johnson K, Corbin AS, Stoffregen EP, Moseson EM, Willis S, Mauro MM, Melo JV, Deininger MW, Druker BJ. In vitro efficacy of combined treatment depends on the underlying mechanism of resistance in imatinib-resistant Bcr-Abl positive cell lines. *Blood* 103:208-215, 2004 [Epub 2003 Aug 21].
6. Corbin AS, Griswold IJ, La Rosee P, Yee KW, Heinrich MC, Reimer CL, Druker BJ, Deininger MW. Sensitivity of oncogenic KIT mutants to the kinase inhibitors MLN518 and PD180970. *Blood* 104:3754-3757, 2004 [Epub 2004 Aug 10].
7. Grossmann AH, Kolibaba KS, Willis SG, Corbin AS, Langdon WS, Deininger MW, Druker BJ. Catalytic domains of tyrosine kinases determine the phosphorylation sites within c-Cbl. *FEBS Lett* 577:555-562, 2004.
8. Corbin AS, Demehri S, Griswold IJ, Wang Y, Metcalf Iii CA, Sundaramoorthi R, Shakespeare WC, Snodgrass J, Wardwell S, Dalgarno D, Iuliucci J, Sawyer T, Heinrich MC, Druker BJ, Deininger MW. In vitro and in vivo activity of ATP-based kinase inhibitors AP23464 and AP23848 against activation loop mutants of Kit. *Blood* 106:227-34 2005 [Epub 2005 Mar3].

9. Crossman LC, O'Hare T, Lange T, Willis SG, Stoffregen EP, Corbin AS, O'Brien SG, Heinrich MC, Druker BJ, Middleton PG, Deininger MW. A single nucleotide polymorphism in the coding region of ABL and its effects on sensitivity to imatinib. *Leukemia* 19(11):1859-62, 2005.
10. Chuah C, Barnes DJ, Kwok M, Corbin A, Deininger MW, Druker BJ, Melo JV. Zoledronate inhibits proliferation and induces apoptosis of imatinib-resistant chronic myeloid leukaemia cells. *Leukemia* 19(11):1896-904, 2005.
11. O'Hare T, Corbin AS, Druker BJ. Targeted CML therapy: controlling drug resistance, seeking cure. *Curr Opin Genet Dev.* 16(1):92-9 2006 [Epub 2005 Dec 15] Review.
12. Schittenhelm MM, Shiraga S, Schroeder A, Corbin AS, Griffith D, Lee FY, Bokemeyer C, Deininger MW, Druker BJ, Heinrich MC. Dasatinib (BMS-354825), a dual SRC/ABL kinase inhibitor, inhibits the kinase activity of wild-type, juxtamembrane, and activation loop mutant KIT isoforms associated with human malignancies. *Cancer Res.* 66(1):473-81, 2006.
13. Demehri S, Corbin A, Loriaux M, Druker BJ, Deininger MW. Establishment of a murine model of aggressive systemic mastocytosis/mast cell leukemia. *Exp Hematol.* 34(3):284-8, 2006.
14. Nguyen TK, Rahmani M, Gao N, Kramer L, Corbin AS, Druker BJ, Dent P, Grant S. Synergistic interactions between DMAG and mitogen-activated protein kinase kinase 1/2 inhibitors in Bcr/abl+ leukemia cells sensitive and resistant to imatinib mesylate. *Clin Cancer Res.* 12(7 Pt 1):2239-47 2006.
15. Griswold IJ, MacPartlin M, Bumm T, Goss VL, O'Hare T, Lee KA, Corbin AS, Stoffregen EP, Smith C, Johnson K, Moseson EM, Wood LJ, Polakiewicz RD, Druker BJ, Deininger MW. Kinase domain mutants of Bcr-Abl exhibit altered transformation potency, kinase activity, and substrate utilization, irrespective of sensitivity to imatinib. *Mol Cell Biol.* 26(16):6082-93 2006.
16. Bumm TG, Elsea C, Corbin AS, Loriaux M, Sherbenou D, Wood L, Deininger J, Silver RT, Druker BJ, Deininger MW. Characterization of murine JAK2V617F-positive myeloproliferative disease. *Cancer Res.* 66(23):11156-65 2006.